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THE AMERICAN REVIEW OF TUBERCULOSIS

A Journal of Pulmonary Diseases

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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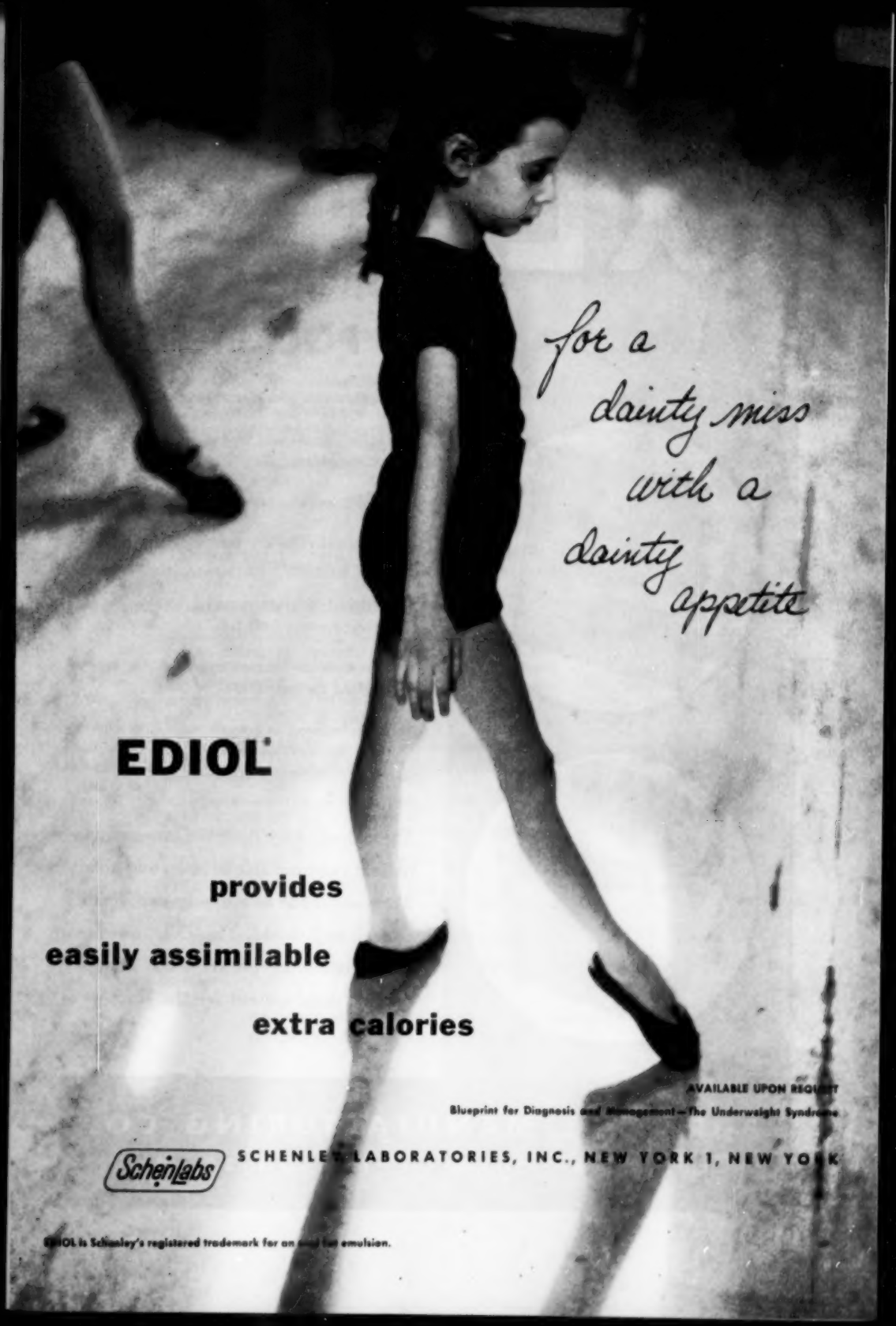
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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tubere. 67:808, 1953.

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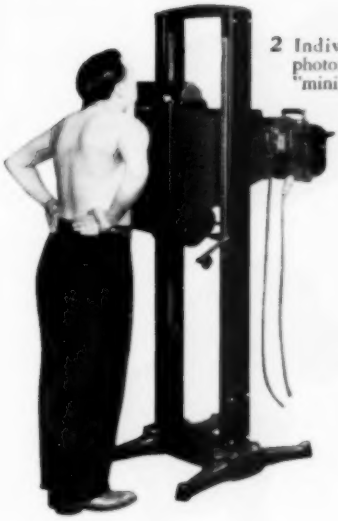

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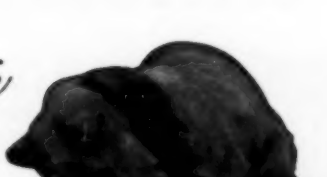

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Letter from the Editor

The editor wishes to take this opportunity to express his appreciation to Dr. William H. Feldman and Dr. Max B. Lurie for their high quality of performance and diligent service as members of the Editorial Board for the past several years. New members of the Board as of July 1, 1954, are Dr. J. Burns Amberson, who has accepted a one-year appointment; Dr. Oscar Auerbach, who has accepted a two-year appointment; Dr. James G. Hirsch, Dr. Kirby S. Howlett, Jr., and Dr. William B. Tucker, who have accepted three-year appointments.

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TENTH ANNIVERSARY OF THE DISCOVERY OF STREPTOMYCIN, THE FIRST CHEMOTHERAPEUTIC AGENT FOUND TO BE EFFECTIVE AGAINST TUBERCULOSIS IN HUMANS[1]

SELMAN A. WAKSMAN

(Received for publication April 19, 1954)

The isolation of streptomycin from a culture of a soil-inhabiting organism, *Streptomyces griseus*, was announced just ten years ago. Among the antimicrobial activities of this substance, those that were most noteworthy were its effectiveness upon gram-negative bacteria and the tubercle bacillus. Soon afterward, its effect in experimental tuberculosis was established, and later its property to ameliorate clinical tuberculosis. Thus started a chain of events which was to culminate in a death blow to the Great White Plague.

Nearly 8,000 papers have since been written on the subject of streptomycin and its utilization in the control of numerous infectious diseases in man and in animals, and more than 30 volumes in many languages have been devoted to it. I shall not attempt to summarize this mass of information, especially since this has already been done in many reviews. I should like merely to tell about certain personal experiences which led to the isolation and development of streptomycin and to its recognition as an important chemotherapeutic agent, especially in the control of tuberculosis.

The two most important aspects of the work done in the Department of Soil Microbiology of the New Jersey Agricultural Experiment Station, Rutgers University, which were largely responsible for the work on antibiotics in general and of streptomycin in particular are: (*1*) the study of actinomycetes, and (*2*) the study of the associative and antagonistic effects among microorganisms in the soil. We first began a systematic study of the actinomycetes in 1914. As a result of these studies, we demonstrated that the soil contains a large population of different microorganisms, comprising many species of actinomycetes. These varied greatly in their morphology and in their physiology. A number of species, including *Actinomyces lavendulae* and *Actinomyces griseus*, were isolated from the soil and described.

The interreactions among soil microorganisms also received considerable attention in our laboratory. The microbes do not live in the soil in isolated com-

[1] From the Institute of Microbiology, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey.

partments but constantly affect the growth of one another. The nature of such action was a constant source of curiosity. Of particular interest were the facts that the actinomycetes are more resistant to adverse conditions than the fungi and bacteria and that the development of the former may repress the growth of the latter.

In 1932, Dr. Wm. Charles White, Chairman of a committee on the microbiology of the soil of the National Research Council[2] and Chairman of the first research committee of the National Tuberculosis Association, asked me to undertake a study of the fate of the tubercle bacillus in natural environments, especially in soils and in water systems. I assigned to this problem one of my graduate students, Chester Rhines. This study lasted three years, at the end of which the following conclusions were reached: (*1*) the avian strain 531 of the tuberculosis organism has a very slow death rate in sewage and in stream-water; (*2*) certain protozoa have the capacity to ingest large numbers of acid-fast bacteria, there being a high degree of specificity in regard to the nature of the protozoa and of the bacteria; (*3*) the avian organism is able to multiply in sterile soil, even in association with some common soil bacteria, but it is slowly destroyed in non-sterilized soil; (*4*) certain fungi are able to repress the development of the tubercle organism in the soil, especially in manured soil.

I could not yet take full advantage of these conclusions. Neither did I take advantage of the observation made, soon afterward, by the poultry pathologist of the N. J. Agricultural Experiment Station, who brought me an agar slant of a culture of *Mycobacterium tuberculosis* which had been killed by a fungus growing upon it. My major interest at that time (1935–1936) was the subject of organic matter decomposition and the interrelations among soil microorganisms responsible for this process.

Finally, in 1939, my own investigations, and especially those of my former student, René Dubos, encouraged me to undertake a comprehensive study of the production by soil microorganisms of chemical substances active against pathogenic bacteria. These substances were later designated as antibiotics. It was natural that I should turn my attention primarily to the actinomycetes, although the fungi and bacteria were not overlooked at first. Gradually, we came to recognize the fact that the first group offered by far the greatest potential source of antibiotics.

The first antibiotic that we isolated, in 1940, from a culture of a soil actinomyces was actinomycin. This substance possessed both bacteriostatic and bactericidal properties. It was active upon a large number of bacteria, including *Mycobacterium tuberculosis*. Unfortunately, actinomycin was so extremely toxic to experimental animals that it offered hardly any potentialities of ever becoming an important chemotherapeutic agent. It may be of interest to note, however, that we observed at that time the fact that actinomycin had a very peculiar effect upon certain organs, notably the spleen, reducing it considerably in size. This observation was recently utilized in Germany, where it has been found that actinomycin has a marked effect in inhibiting the development of the lymphogranuloma type of tumors, known as Hodgkin's disease.

[2] See report of National Research Council for 1931–1932, page 41; 1932–1933, page 28.

Another two years passed in a search for less toxic and more desirable antibiotics. Several antimicrobial substances were isolated and set aside because of a certain toxicity or limited activity. Meanwhile, the methods for the study of antibiotics were perfected and we learned to recognize different types of substances. In 1942, streptothricin, a substance which possessed great potential antimicrobial properties, was isolated from another culture of a soil actinomyces. It was much less toxic than actinomycin and was active upon a large number of pathogenic bacteria, including both gram-positive and gram-negative organisms. It was water-soluble and heat-stable, and was active in suppressing various infections in experimental animals. It possessed, however, a slight delayed toxicity upon the animal system. Meanwhile, we continued our screening program, concentrating largely upon the actinomycetes, and, before we proceeded with the clinical evaluation of streptothricin, we isolated streptomycin, in 1943, from still another soil actinomyces.

Early in June, 1943, Dr. Florence B. Seibert of the Henry Phipps Institute supplied me with a mass of living and dead cells of *Mycobacterium tuberculosis* for soil enrichment experiments, to stimulate (as we then thought possible) the development of organisms producing antituberculous agents.

About that time, on June 1, 1943, I attended a conference called by Dr. White, and attended by Dr. Leroy U. Gardner and certain others interested in chemotherapy of tuberculosis, to discuss the study of the effect of bacteriostatic substances upon the tuberculosis organism. I well recall that Dr. White had the idea of obtaining active preparations from earthworms, which were said to be able to digest the tubercle bacillus. This idea was based upon the potential action of enzyme systems, which scarcely appealed to me. I urged that consideration be given, instead, to antibiotics.

The streptomycin-producing culture of the actinomyces was first isolated from the swab of a chicken's throat on August 20, 1943. It belonged to a group of actinomycetes that we described in 1916 as *Actinomyces griseus*. Although this name was first used for a culture isolated by Krainsky in Russia in 1914, it was doubtful whether the two cultures were identical, since the comparisons were made only upon published descriptions. We found *A. griseus* widely distributed in the soil and I used it in some of the physiologic studies for my doctor's thesis in 1916–1917.

In January, 1943, Dr. Henrici and I decided to create a new genus of the aerial mycelium producing species of actinomycetes, and designated this genus *Streptomyces*. As a result of this, *Actinomyces griseus* became *Streptomyces griseus*, and we had a name for a new antibiotic. The announcement of the isolation of streptomycin was published in January, 1944.

It was soon demonstrated that streptomycin was a drug of low toxicity and that it was active in experimental animals against a large number of infectious diseases caused by gram-positive and gram-negative bacteria. It was so similar however, to streptothricin that for a long time we studied the two antibiotics side by side. Gradually, however, we concentrated on streptomycin because of its lower toxicity.

In describing the properties of streptomycin as a chemotherapeutic agent, I would like to emphasize particularly its activities against tuberculosis. The sequence of events can best be described by citing certain correspondence of Dr. William H. Feldman and Dr. H. Corwin Hinshaw, of the Mayo Clinic.

Dr. Feldman first visited my laboratory early in November, 1943. He was very much interested in our program, particularly the antimicrobial activities of the *Streptomyces* antibiotics as well as "the possibilities of carrying out some cooperative studies if and when you obtain an agent which you think would be worthy of *in vivo* application." I advised him early in March, 1944, that we might soon be able to send him some streptomycin. He at once expressed his readiness to test the action of this agent in experimental tuberculosis in guinea pigs. Recognizing that only limited quantities of the substance were available, he believed that even with small amounts he could obtain some rather definite information regarding the possible ability of streptomycin to influence favorably experimental tuberculosis.

In a letter, dated April 27, Feldman wrote that the animal studies were already started. (I might say that this first animal experiment was carried out with material that had only 58 units or micrograms per milligram, or 5.8 per cent purity.) Seven days later, or on May 4, he was able to state:

> This morning I checked on the guinea pigs which have been receiving streptomycin for the past week. One animal is receiving 75 mg. daily and the other 37.5 mg. daily; the medication being given five times each twenty-four hours. Both animals look exceedingly well, although both have an area of induration of moderate degree at the site where the substance has been injected. We are now going to increase the dosage of the one animal receiving the smaller dose so that both will be receiving 75 mg. daily. Next week we are going to start two additional guinea pigs on the substance. These were inoculated with tubercle bacilli on the same day as the first two mentioned.

Simultaneously, Feldman urged me to send some streptomycin to Dr. Fordyce R. Heilman so that its effect could be evaluated against various pathogenic bacteria. This I gladly did with the result that Heilman succeeded in establishing the effectiveness of streptomycin in infections due to *Pasteurella tularensis* and *Klebsiella pneumoniae*. At that time I wrote Dr. Feldman:

> In view of the fact that there is a great similarity in the action of streptothricin and streptomycin, the effectiveness of the two substances *in vivo* should be considered side by side. I may add here that another laboratory has already been studying the use of streptothricin in the treatment of animals infected with *M. tuberculosis*.

July 10, 1944, was a historic date. On that day Feldman and Hinshaw came to see me to discuss the results of the first animal experiments and to plan clinical treatment of tuberculosis. I promised to solicit the collaboration of Merck & Co. to begin immediately the preparation of additional quantities of streptomycin. All of us were of the opinion that this must be kept highly confidential so as not to arouse undue public optimism.

On July 19, 1944, Feldman wrote:

> You will be interested to know that the guinea pigs received their infecting dose of tubercle bacilli yesterday morning and their first dose of the respective medicants, streptothricin and streptomycin, at 6:00 last evening. The dose schedule calls for an injection every 6 hours. So far we have been unable to obtain any additional laboratory assistance so Doctor Hinshaw and I have taken over the task of administering the substances. We felt that if we were to wait until we got help the program might be delayed indefinitely. We consider knowledge of streptothricin and streptomycin as privileged information, so much in fact, that we do not use the terms in the laboratory but refer to them as A_1 and A_2. I agree with you that it would be very unwise to have the information reach the public prematurely.

These studies confirmed our own observations of the greater toxicity of streptothricin, as well as the variable toxicity of different lots of streptomycin.

On September 19, Feldman was able to report that the sixty-day *in vivo* tests were completed September 17:

> The results were indeed gratifying, as a study of the necropsy protocols clearly shows. The amount of severe and widely disseminated tuberculosis in the controls left no doubt regarding the lethal capacity of the infecting organism. In the treated group, definite signs of tuberculosis were absent in almost every instance, insofar as involvement of the parenchymal organs were concerned. The disease when present consisted of residual foci at the site of inoculation, the contiguous axillary lymph nodes, or the tracheobronchial lymph nodes. The two short-time experiments have thus answered about all the questions that we had in mind for demonstrating the ability of streptomycin to cope successfully with tuberculosis introduced in guinea pigs at the time treatment began. The fact that some of the animals were infected two weeks before treatment began does add important information. Of course the real test of the substance, insofar as tuberculosis of guinea pigs is concerned, is now being done in the long-time experiment.

Six weeks later (October 31), Hinshaw presented before the Tuberculosis Subcommittee of the National Research Council, members of the U. S. Public Health Service, representatives of the National Tuberculosis Association, Army and Navy, and certain liaison officers of foreign governments, meeting in Washington, the results of their experiments on streptomycin. He wrote to me soon afterward:

> I continue to hear from underground sources that information concerning the potentialities of streptomycin in tuberculosis has been rather widely disseminated and I certainly hope that your paper on *in vitro* effects can be published at an early date to be assured of your due priority in this matter. Doctor Feldman and *I* are also eager to get at least a preliminary note concerning the *in vivo* work into the literature as soon as possible for the same reason. We feel sure that this can be accomplished by a simple factual report, which should not arouse any enthusiasm on the part of newspaper reporters and others, and possibly workers should know the facts in order to protect them from some of the wild rumors which are being circulated. In Chicago this week I heard the rumors that streptomycin is being employed in clinical tuberculosis on a large scale with marvelous results. I feel very sure that this is not true, and when facts are lacking fancy is so often substituted freely, even in so-called scientific circles.

Within one year after the announcement of the discovery of streptomycin (January 23, 1945), Hinshaw wrote to Dr. Chester Keefer, urging him that everything possible be done to expedite the production of streptomycin in quantities sufficient for adequate clinical tests in tuberculosis and that it be judiciously allocated. A few days later (January 29) a telegram reached me from Feldman: "Long term crucial experiment streptomycin terminated today. Incomplete results indicate impressive therapeutic effects."

Hinshaw was meanwhile maintaining two patients on streptomycin. He wrote on March 9, 1945:

> The results are sufficiently encouraging to be tantalizing, and we cannot avoid the feeling that if we could give a million or more units a day we might have something more impressive.

On August 25, he was able to report:

> We have now treated a total of thirty-three patients, including those who are now under hospitalization, and continue to be quite optimistic. Dr. Esmond Long and Dr. Henry Sweany spent an entire day going over every single case that has received streptomycin. They expressed an unqualified opinion that early extensive lesions of tuberculosis of the so-called hematogenous type are reversed to an unmistakable degree. As a result of their survey they are planning to undertake the treatment of tuberculosis in the Army with streptomycin, setting up a group at Fitzsimons General Hospital and at Burns General Hospital in the very near future.

This was followed on October 5, by a letter from Feldman:

> Observations regarding the clinical application of streptomycin continue to be cause for enthusiasm. New information is constantly being assembled and of course we feel very fortunate in being permitted to continue our studies in spite of the fact that the War Production Board has taken over the allocation of streptomycin. We feel very important, indeed, that the authorities saw fit to permit our work to continue in spite of the fact that the supply for other civilian uses has been curtailed or perhaps cut off.

Hinshaw added on December 11:

> I believe that we now have undeniable clinical and pathological evidence that streptomycin does modify the course of tuberculosis in man in a favorable direction, but the magnitude of this effect, its permanence and its applicability to the common varieties of pulmonary tuberculosis are matters which must be left undecided until the drug is produced in adequate quantity for long-term treatment.

These first experiments soon began to make history. The most spectacular results were obtained with the use of streptomycin in the treatment of miliary tuberculosis, tuberculous meningitis, tuberculosis of the larynx, bone and joint tuberculosis, pulmonary tuberculosis, and various other forms. To quote further from the letters of Hinshaw and Feldman,

> Streptomycin has been found to possess most of the characteristics required of a successful antibacterial agent for the treatment of human disease. It pos-

> sesses a range of antibacterial action *in vitro* not paralleled by any other available substance. It may be administered by any of the usual parenteral routes conveniently. It maintains its activity *in vivo* and appears to diffuse from the blood stream into most of the tissues. It is of very low toxicity for man and the few unfavorable side reactions which have been observed have been attributed to impurities. It possesses activity against many organisms which are relatively insensitive to penicillin, including a number of pathogenic, gram-negative, gram-positive, and acid-fast bacteria. Much more study and observation will be required to define the possibilities and limitations of streptomycin therapy in cases of tuberculosis, but preliminary observations are sufficiently extensive and appear to be sufficiently encouraging to justify such investigative projects when supplies of the drug permit. In the meantime it is important to emphasize the limitations of streptomycin in treatment of tuberculosis, limitations which are at least in part due to the nature of the disease.

On January 1, 1946, Walsh McDermott and Carl Muschenheim and their associates at the New York Hospital-Cornell Medical Center also started an investigation of streptomycin in tuberculosis in humans. Except for the initial weeks, their study was conducted under the auspices of the Keefer Committee of the National Research Council. On the basis of this study, they were able to report a complete confirmation of the Hinshaw-Feldman studies in humans in June at the annual meeting of the National Tuberculosis Association in Buffalo.

Indeed, I received a telegram dated June 12, 1946 from Buffalo, signed by Feldman and Hinshaw which read: "Our streptomycin studies reported at National Tuberculosis Association here fully confirmed experimentally and clinically establishing this as first effective chemotherapeutic remedy for tuberculosis. Hearty congratulations."

On September 7, 1946, the Committee on Chemotherapeutics of the National Research Council under the Chairmanship of Dr. Keefer reported the results of the first 1,000 cases of different infectious diseases treated with streptomycin. On December 12, the first Streptomycin Conference of the Veterans Administration was held in Chicago. Reporting on this Conference, Hinshaw wrote:

> The results are most consistent and precisely like those which we have secured here. As a result of this presentation, it has been arranged that nineteen hospitals in the Veterans Administration will be using streptomycin on all suitable cases immediately and before many weeks the drug will be made available for treatment of tuberculosis in all the remaining Veterans Administration hospitals. It begins to look as though practical application of the drug is somewhat ahead of our knowledge of many fundamental problems, but this is probably better than to have the problem lagging behind.

The rest is history. It was thus definitely established that chemotherapy of tuberculosis is possible, that the Great White Plague can be treated by means of drugs just as can numerous other infectious diseases of man and animals. Streptomycin pointed the way. Although the methods of treatment of various forms of tuberculosis have undergone marked changes since the first successful use of this antibiotic in 1945 and in 1946, streptomycin is still the basis of all tuberculosis therapy. It is now used successfully with para-aminosalicylic acid

(PAS) and with various forms of isoniazid. The supplementary use of these synthetic compounds has reduced the toxicity of streptomycin and the development of resistance by the tuberculosis organism.

From a few grams in 1944 and in 1945, streptomycin production has grown into a great industry. In 1953, in the United States alone, nine companies manufactured 15 to 20 million grams a month. There are two companies in Great Britain, one in Sweden, one in Denmark, three in France, one in Germany, three in Italy, two in Spain, four in Japan, and possibly several countries behind the iron curtain engaged in the manufacture of streptomycin. From $25.00 a gram in 1946, the bulk price has been reduced to less than 25 cents a gram.

Although streptomycin is used largely in the treatment of diseases of the tuberculosis type, considerable quantities are also employed, alone or in combination with penicillin or other antibiotics and synthetic compounds in the treatment of numerous other infectious diseases of man and of animals. Streptomycin has also found many other applications, as in the preservation of virus vaccines and of semen of animals and in the treatment of certain plant diseases.

I need hardly dwell here upon the numerous problems involved in the development of streptomycin, not all very simple. I need only mention the problems of the active strains of *S. griseus*, the methods of isolation of streptomycin from the broth and its further purification, the problems of standardization of streptomycin for therapeutic use, the determination of its activity against microbes and the problems of its toxicity to animals and then to humans, the danger of development of resistance among sensitive bacteria, and a host of others that were bound to come up in the development of a successful chemotherapeutic agent. Neither will I dwell upon the problems of manufacture, relations with foreign manufacturers, the patent situation, the establishment of the Rutgers Research and Endowment Foundation, although these were all highly significant.

One may rightfully say that a new era has been opened by the introduction of streptomycin in chemotherapy. It was later followed by the isolation in various other laboratories of numerous antibiotics from cultures of actinomycetes. It may truthfully be said that, since the discovery of penicillin, all the important antibiotics for the treatment of infectious diseases have been found to be produced by actinomycetes.

Perhaps no more fitting commemoration of the tenth anniversay of the discovery of streptomycin is possible than the dedication of the Institute of Microbiology, which took place on June 7 of this year.

HISTORICAL NOTES ON EARLIEST USE OF STREPTOMYCIN IN CLINICAL TUBERCULOSIS

H. CORWIN HINSHAW[1]

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The tenth anniversary of streptomycin prompts the publication of certain reminiscences concerning the early clinical trials of this epic-making substance. Within the span of the calendar year of 1944, the discovery of streptomycin was announced, the effectiveness of the drug against experimentally produced tuberculosis was published, and clinical trials were instituted. The preliminary clinical results were published in September of 1945.

Throughout the period of early clinical study and during the years which have followed, the scientific wisdom of Dr. William Feldman has been a constant guiding force in our clinical projects and the keen interest of Professor Waksman a stimulating factor.

Streptomycin was made available to us at a propitious time, Dr. Feldman and I having been engaged in the study of other antituberculosis drugs during the previous five years (1). Clinical studies in collaboration with Dr. Karl Pfuetze and other associates had already involved more than one hundred patients treated with a drug of the diamino-diphenyl sulfone series during 1941 and 1942 (2). Although sulfonamide drugs had failed, we had been encouraged by results attained with the diamino-diphenyl sulfone derivatives. In retrospect, I am convinced that we observed true chemotherapeutic response with these drugs, but we were too timid to say so (3). Had they not been supplanted by superior substances, the sulfones might have developed into potent remedies against tuberculosis. Their present-day efficacy in the treatment of human leprosy was a product of these studies in tuberculosis, and it is now demonstrated that long-continued treatment with these rather toxic compounds is feasible. A heterocyclic sulfone, now known as Promizole®, had occupied our attention during the time immediately prior to the discovery of streptomycin. A controlled clinical study of Promizole® in the treatment of pulmonary tuberculosis was completed during 1944 and never published because results were not considered to be convincing.

The chemotherapeutic studies in tuberculosis prior to the discovery of streptomycin developed methods which were immediately applied to the evaluation of streptomycin. Laboratory procedures were devised which permitted valid comparisons between drugs (4) which have been used subsequently by many investigators. Recommendations for clinical investigation based on studies of sulfone drugs were recorded, which are still applied.

The first clinical report of streptomycin in tuberculosis concerned thirty-four treated patients and was published on September 5, 1945, scarcely more than a year after the effect of the drug upon tuberculosis of experimental animals

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was demonstrated. The report was brief, only five pages, and the potential effect of each word was carefully weighed by Dr. Feldman and myself, for we could foresee the tragedy of any premature optimism by the general public (5). Since this publication is rarely cited, it is appropriate to quote from it rather extensively, especially since many of the conclusions are applicable ten years later.

Concerning toxicity of streptomycin we wrote:

> Streptomycin is a drug of low toxicity for man and the doses described. . . have rarely caused any serious reactions, even when continued for several weeks without interruption. There is usually some pain at the sites of repeated injections but this is no more severe than that produced by penicillin. Frequently there is a moderate elevation of the patients' body temperature but we have not regarded this as being of serious significance. Some inadequately purified materials have produced a response resembling that produced by histamine, including throbbing headache and flushing of the skin soon after the injection. Such lots of streptomycin are unsuitable for clinical use. Most patients complain of mild malaise, aching in various muscles and rarely more severe arthralgia attributed to streptomycin or impurities contained therein. Since we have usually limited our studies to those patients whose immediate prognosis was unfavorable, these symptoms have been well borne. We have noted less severe reactions recently now that more purified preparations have been made available in recent months.
>
> We have noted in four patients an apparent acquired sensitization to preparations of streptomycin with violent febrile reactions when therapy was resumed after an interval of a few weeks, following a previous course of treatment. In each instance desensitization was readily accomplished by administering small doses at first, followed by doses of steadily increasing quantity.
>
> We have observed one case of transient deafness and three cases in which there were apparent disturbances of function of the vestibular apparatus when large doses were administered for prolonged periods. It is not known if streptomycin or some impurity produced these symptoms and the possibility of tuberculosis being a factor is not yet excluded in all cases. We have tentatively ascribed these symptoms to a selective neurotoxic effect on the eighth cranial nerve.

Concerning dosage we wrote:

> The dose of streptomycin has not been accurately determined for various types of tuberculosis but we have regarded 800,000 S units per twenty-four hours as the minimal therapeutic dose. Usually patients have received 1,000,000 to 2,000,000 S units per day and in rare and urgent circumstances higher doses have been given.

This is equivalent to 1 or 2 gm. of streptomycin daily.

Treatment of pulmonary tuberculosis was described thus:

> Sixteen patients who had pulmonary tuberculosis have been treated, some in collaboration with Dr. Karl Pfuetze (Mineral Springs Sanatorium) and others with our associate, Dr. Robert Glover. These patients have been treated for periods of from one to three months and eight of these have been observed subsequent to treatment for periods up to four months. It is important to note that streptomycin did not appear to have any rapidly effective curative action in these cases but that extensive and progressive lesions of known recent origin have tended to improve promptly in a manner which resembles the natural processes of healing. This is especially apparent in fine, widely distributed lesions which appeared to be of hematogenous distribution. The sputum of patients who have

common types of chronic fibrocaseous tuberculosis may remain positive indefinitely and regions of fibrosis and cavitation may not disappear despite large doses of streptomycin. More acute and finely distributed lesions may appear to resolve but such changes are not demonstrable on roentgenographic examination in less than three to six weeks and reasonably complete resolution is likely to require two or three months or longer. When treatment has been discontinued, prompt reactivation of the process has been observed in a few instances, lending further support to the hypothesis that a bacteriostatic rather than a complete bactericidal effect of the drug has been realized.

The study of pulmonary tuberculosis is hampered by the fact that roentgenographic shadows are only a rough measure of the extent of the disease and the character of the pathologic changes can be calculated only crudely with no thoroughly dependable criteria to indicate true healing. It will be immediately obvious to those who are familiar with the course of pulmonary tuberculosis that the present series of cases is inadequate in size and that longer periods of observation will be required before definite conclusions can be drawn. A more extensive and more closely controlled study of the effect of streptomycin on pulmonary tuberculosis is under way and will be reported subsequently.

Miliary tuberculosis and renal tuberculosis therapy with streptomycin was described as follows:

Two patients who had early miliary tuberculosis and one of whom had renal tuberculosis have shown unmistakable and striking improvement in the roentgenographic appearance of the lesions in the lungs. The clinical improvement noted in these patients has not paralleled that observed in roentgenograms of the lungs and it is probable that the disease has become localized in some inaccessible regions of the body. One of these patients has been observed for six months and one for only two months. A third patient who had miliary tuberculosis with meningitis was treated for five days prior to death. Detailed reports will be published in collaboration with Dr. R. L. J. Kennedy and Dr. L. F. Greene after further study and observation.

Five patients, each with a solitary kidney and with tuberculosis of the genitourinary tract, as demonstrated by consistent presence of tubercle bacilli in the urine, have been treated with streptomycin. One of these patients has been mentioned in the preceding paragraph. The tubercle bacilli disappeared from the urine on microscopic examination within two to four weeks in four of the five cases. The four patients who responded to treatment in this encouraging manner have now been followed for one to four months since cessation of treatment and on microscopic examination the urine remains negative for tubercle bacilli. No tubercle bacilli have as yet been demonstrated by culture or guinea pig inoculation from the urine of any of these four patients subsequent to treatment but sufficient time has not elapsed to complete all of these examinations. The one remaining patient, who continues to have tubercle bacilli in the urine, also has miliary tuberculosis but, as mentioned previously, the latter lesions have markedly improved so far as can be determined by roentgenograms of the lungs.

The response of cutaneous sinuses was well shown and described thus:

Three had draining sinuses due to suppurative tuberculous lymphadenitis and showed very prompt and striking response to therapy, especially in two of the three cases. We are mindful of the tendency of such lesions to recur and we shall report the subsequent clinical course of these patients with our associates in dermatology in due time.

The paper concluded with an unconventional appeal:

> It is to be ardently hoped that if these results are noticed by lay persons, they will interpret the results in the same cautious frame of mind that scientific investigators have endeavored to maintain. This unusual suggestion is made for the benefit of the many thousands of patients who have tuberculosis. Morale plays a crucial part in treatment of such a debilitating and chronic disease and morale is injured by premature and optimistic reports of results which may not be sustained in practice. No one as yet actually knows what the final judgment will be concerning the effect of streptomycin on clinical tuberculosis.

Publicity was unavoidable when evidence appeared that a specific drug had been developed against the most important infectious disease of the human race: tuberculosis. Newspaper and magazine writers appeared sympathetic with our desires to avoid the cultivation of false hopes by patients, yet each assignment to get the latest story on streptomycin had to be fulfilled. We adhered consistently to a rule that no personal interviews would be granted. All press conferences were those conducted by medical and scientific societies, with as many participants as possible, hoping thereby to dilute the personal factor. Unfortunately, many societies permit the release of popular articles before scientific publications have made the information available to physicians who are called upon to interpret the facts to their patients.

We believed then and now that personal publicity is detrimental to scientific reputation and that the favorable opinions of physicians and scientists should be the objective of the research worker. None of the magazine articles was written with our consent or cooperation, and determined efforts by ourselves and our associates at the Mayo Clinic succeeded in preventing publication of some others which came to our attention in time to take action.

Desperate patients, their relatives, and physicians from many countries throughout the world sought to obtain streptomycin when none was to be had or when it could be put to better use. A committee of the National Research Council under the able leadership of Dr. Chester Keefer bore the brunt of many of these urgent and sometimes hysterical appeals. Dr. Keefer deserves great credit for conserving supplies of this rare and priceless substance at a critical time. Our clinical advice was sought and gladly given through hundreds of letters, telegrams, cablegrams, and long distance telephone calls during a period of many months. Transoceanic telephone calls were received from several European countries, including some from Russia, from South America, Africa, and Australia. Each communication received a personal reply, and form letters were not resorted to, even to save valuable time. Patients were urged to follow the advice of their personal physicians and reminded of the value of conventional treatment methods. Many forms of political and economic pressure were applied to secure the life-saving drug, and a lively international traffic in contraband streptomycin is believed to have developed.

Some human dramas associated with the early clinical experiments cannot be revealed lest privileged information be divulged. A few moribund patients received injections of material containing many impurities, and no harm could

be detected at subsequent autopsy. Temporary amelioration of symptoms was sufficiently convincing to encourage more energetic therapy of subsequent patients, especially after Merck & Co., Inc., were able to supply streptomycin of constantly improving quality and in increasing quantity. For several months, all streptomycin released for tuberculosis therapy was assigned to our group, but before long another clinical research project was authorized at Cornell University under the direction of Dr. Walsh McDermott.

During the earliest and most uncertain phases of our clinical study at the Mayo Clinic, each patient or his relatives were carefully apprised of the nature of streptomycin and the logic prompting its use. Treatment was never urged in the face of any hesitation or doubt to submit to treatment, and the experimental nature of the project was never disguised. We made it a point to state literally that the patient was to be used as a "human guinea pig." Nevertheless, acceptance was almost universal, and the hope expressed was that the experiment would at least benefit others, as it surely did. These patients were true collaborators and deserve to be ranked as heroes. The experience confirmed a long-held belief that intelligent, private patients, honestly informed of the facts, constitute superb experimental subjects.

After convincing evidence of the clinical value of streptomycin in potentially lethal forms of tuberculosis appeared, my colleagues and I were urged by relatives, on a few occasions, to discontinue treatment which seemed to be merely prolonging life and agony. This we opposed on moral and ethical grounds, and subsequently, when recovery ensued, the gratitude of the patients and their relatives was almost pitiful to observe.

Our most dramatic emotional experience was at the meeting of the National Tuberculosis Association in Buffalo, New York, in May of 1946, when we presented our first clinical report on streptomycin to a national audience. We feared that disbelief of the results would be expressed because of the many previous false hopes raised by other "cures" throughout all previous medical history. Shortly before delivering the paper, I learned that Dr. Walsh McDermott was to discuss the report, but did not know what attitude would be expressed. When we learned that Dr. McDermott and associates had fully and independently confirmed the findings and when his discussion was so forthright and convincing, Dr. Feldman and I were overjoyed and sent the telegram to Dr. Waksman, which he has quoted. The prestige added by the Cornell report did much to promote immediate and serious study in this field, and immediately after the Buffalo meeting, a conference with military and veteran's authorities was held in Washington, D. C. At this conference we presented our data, and the plans were formulated for expansion of the study.

Welch and Lewis (6) state that the early studies cited ". . . initiated the most extensive studies of a single drug in a single disease every undertaken." In 1946, a series of investigations was supervised by a committee of the American Trudeau Society, made possible by a gift of a quantity of streptomycin by the manufacturers which was currently valued at one million dollars. Very soon the initiative was passed to the Veterans Administration, under the leadership of Dr. John

Barnwell and Dr. Arthur Walker. This project involving hundreds of investigators and many thousands of patients has grown and prospered to become an unparalleled phenomenon in cooperative medical research. The thirteenth national conference of this group, held in February, 1954, indicated that many productive fields of research remain open (7).

Since the discovery of streptomycin, tuberculosis death rates in the United States have been reduced to approximately one-third of their former toll. No physician who cares for patients with tuberculosis will doubt that modern therapy deserves a large share of the credit for the survival of these many thousands of persons. We, who by chance happened to be involved in this development, are humbly grateful for a privilege which comes to few men. Had our previous work taken a different turn, others with greater ability and resources might have accomplished these goals more efficiently.

Having spent much of my professional life in the field of general internal medicine and in the laboratory sciences, I have come to know physicians, surgeons, and scientists engaged in many activities throughout the world. Among these, the men engaged in tuberculosis work have appeared singularly dedicated to the broad idealism of cooperative endeavor for the benefit of mankind. These attributes of the hundreds of investigators concerned in the development of streptomycin and auxiliary drugs during the ten years past have resulted in harmonious teamwork unequaled in the history of medical achievement.

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THE AFTER-HISTORY OF PULMONARY TUBERCULOSIS[1]

III. Minimal Tuberculosis

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INTRODUCTION

The present study was undertaken to determine the clinical course of a group of persons with minimal pulmonary tuberculosis. Each person was admitted to study on the date of diagnosis and his clinical course was assessed at subsequent yearly intervals. The observations are combined to form a composite after-history in a manner which permits general conclusions to be drawn (1).

MATERIAL

A review was made of all original diagnoses of minimal pulmonary tuberculosis made by the hospital staff during the years 1937 through 1947. In no case had a diagnosis of pulmonary tuberculosis been previously made. The review included only persons whose established residence at the time of diagnosis was in one of the eight semi-rural counties served by the hospital.

Two physicians,[2] independently of one another and without knowledge of the subsequent clinical course, classified the diagnostic chest roentgenogram of each case according to the presence of pulmonary tuberculosis and the stage of disease. The classification of the stage of disease was based on the *Diagnostic Standards* (1940 edition), published by the National Tuberculosis Association (NTA). In the few cases in which there was disagreement, consultation was held to effect a mutually acceptable decision.

The classification of the cases is shown in table 1. It is of interest that, of the 196 cases considered either not to be pulmonary tuberculosis or to represent only pulmonary calcification, none has since been reported to the hospital as a case of tuberculosis.

The clinical status of each case at the time of diagnosis was assessed on the basis of roentgenographic and bacteriologic data collected during the six months following diagnosis. This assessment reflects, with few exceptions, the opinion formed at the time by the hospital staff. Fifty-four cases were excluded from study because the length of observation was less than a full year and sufficient data were not available on which to assess the clinical status. On the other hand, 18 patients were included in the present study who were first reported as cases of advanced tuberculosis but whose diagnostic chest roentgenograms actually showed minimal disease.

[1] From Hermann M. Biggs Memorial Hospital, Ithaca, New York.

[2] We acknowledge with gratitude the assistance of Dr. H. Charles Ellsworth in interpreting the roentgenograms.

TABLE 1

CLASSIFICATION OF CASES WITH DIAGNOSIS OF MINIMAL PULMONARY TUBERCULOSIS

Total number of diagnoses reviewed	753
Total number of cases excluded from study after review	269
Reasons for exclusion	
No significant pulmonary disease	110
Nontuberculous pulmonary disease	22
Pulmonary calcification only	64
Moderately advanced tuberculosis	73

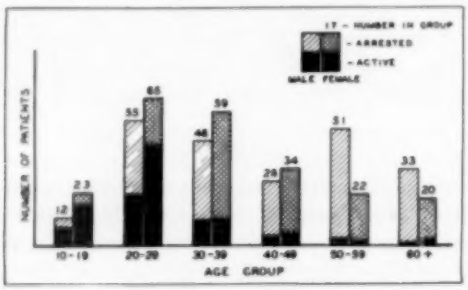

FIG. 1. Minimal tuberculosis: age, sex, and status at diagnosis

Thus the clinical material consists of 448 patients who were discovered to have minimal pulmonary tuberculosis during the eleven years from 1937 through 1947 and who were followed until 1951. One hundred and thirty-four patients were considered to have active disease at the time of diagnosis, of whom 128 have had at least one sputum examination for tubercle bacilli. Up to the present time, 112 have had at least one "positive" sputum by some method. Three hundred and fourteen patients were considered to have arrested disease at diagnosis, of whom 97 have had at least one sputum examination. Thirty-seven of these have been found to have sputum positive for tubercle bacilli by some method, usually after clinical relapse occurred.

Despite the paucity of bacteriologic confirmation in the patients classified as having arrested disease, the abnormal roentgenographic shadows may reasonably be interpreted as pulmonary tuberculosis. Endemic histoplasmosis is infrequent in the hospital district and, since a relatively static population inhabits this area, a significant number of immigrants with pulmonary histoplasmosis would not be expected. The same reasoning applies to coccidioidomycosis.

In figure 1 may be seen the distribution of the patients by sex, as well as by age and clinical status at the time of diagnosis. This reflects the common clinical experience with minimal pulmonary tuberculosis, namely, that a group of patients with active disease usually includes a greater proportion of young people and a greater proportion of females than a group with arrested disease (2, 3). Included in the study were one American Indian, 5 Negroes, and 442 whites.

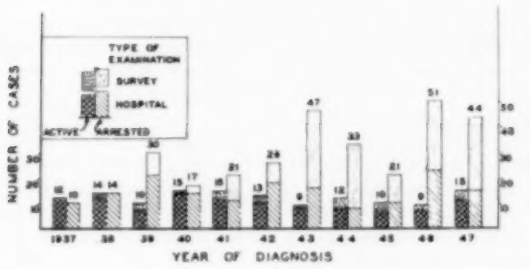

FIG. 2. Number of diagnoses each year. Minimal tuberculosis by status and type of examination.

In figure 2 the number of admissions to study during each calendar year are presented, divided according to the clinical status as well as to the type of examination by which diagnosis was established. The hospital diagnoses are those made by the medical staff on patients referred by private physicians because of symptoms or contact with a known case of tuberculosis. The survey diagnoses are those made by means of roentgenographic surveys of groups of apparently healthy people and by Selective Service preinduction chest photofluorograms.

The material in figure 2 is of more than casual interest in that the annual number of diagnoses by the hospital staff remains relatively constant throughout the eleven-year period. On the other hand, in the latter half of the period there is a significant increase in the number of survey diagnoses.

The patients with survey diagnoses differed from those with hospital diagnoses in several respects. Whereas fully two-fifths of the patients with hospital diagnoses were considered to have active disease on admission to study, only one-seventh of those with survey diagnoses were classified as having active disease on admission. The group of patients with survey diagnoses includes twice as many males as females while the group of hospital diagnoses includes nearly twice as many females as males. The median age of the patients with survey diagnoses is eighteen years above the median age of the patients with hospital diagnoses. It is somewhat anomalous that, in contrast to the steady incidence of active cases over the eleven-year period, there was a fall in the hospital district tuberculosis death rate from 24 per 100,000 to 14 per 100,000. At the present time this death rate is approximately 8 per 100,000, and the current incidence of active minimal tuberculosis is comparable to that observed during the earlier eleven-year period. The steady incidence of active cases of minimal disease cannot be explained by an increase of the population of the hospital district since this rose only 3.5 per cent during the period of study. Furthermore, there was no increase (actually zero per cent) in the annual number of new patients referred for examination because of symptoms or contact.

It may be seen in table 2 that the median age of the patients with arrested tuberculosis increased during the later years of the study, a fact that can readily be explained by the rising influx of older patients with survey diagnoses. How-

TABLE 2

MEDIAN AGE OF PATIENTS WITH MINIMAL TUBERCULOSIS CLASSIFIED BY STATUS AT DIAGNOSIS AND YEAR OF DIAGNOSIS

YEAR OF DIAGNOSIS	STATUS AT DIAGNOSIS	
	Active	Arrested
Total	24	42
Male	26	45
Female	23	39
1937–1938	22.5	38.5
1939–1940	24.0	38.0
1941–1942	23.5	39.0
1943–1944	23.0	41.0
1945–1946	27.0	44.0
1947	27.0	49.5

ever, the median age of the patients with active disease also rose, a fact which cannot be explained on the same basis.

Method

At the time of diagnosis and at annual intervals (anniversaries) thereafter, each patient was assigned to one or another category on the basis of information obtained from the medical record. With few exceptions, the clinical status assigned by the writers to a patient at a given anniversary corresponds to that recorded by the hospital staff on the basis of the NTA *Diagnostic Standards* (1940 edition). If the condition of a patient changed between two anniversaries, his new status was assigned at the latter anniversary. The categories are as follows:

Arrested: For six months or more prior to the anniversary, the patient's sputum has been free of acid-fast bacilli and his serial chest roentgenograms have been compatible with stable disease. When more than a year has elapsed between clinic examinations and the chest roentgenograms show a stable lesion, the patient is continued in the arrested category throughout the interim.

Presumably arrested: The patient is known to be well and working full time but has not had a recent chest roentgenogram. The latest available roentgenograms are compatible with a stable lesion. In the event that a lapse of more than a year without examination precedes evidence of reactivation, the patient is assigned to the presumably arrested category during the interim.

Active: Within six months prior to the anniversary, the patient's sputum may have contained acid-fast bacilli but, if not, serial chest roentgenograms have shown unstable disease.

Died—tuberculosis: During the year prior to the anniversary the patient died of progressive tuberculosis.

Died—nontuberculous cause: During the year prior to the anniversary the patient died of causes known to be other than tuberculosis.

Lost: The patient became permanently lost to follow-up during the year prior to the anniversary.

Incomplete: The patient is alive and traced at that anniversary which occurs in 1950, but he was admitted to study too recently to complete ten years of follow-up.

Accordingly, he is assigned either to the active, the arrested, or the presumably arrested category at his 1950 anniversary and to the incomplete category at his next succeeding anniversary. No use is made of information relating to changes of status which occur after the 1950 anniversary.

In table 3, columns (2)–(7) and (9) show the number of patients assigned to the various categories at each anniversary. In an earlier paper (1), it was pointed out that under certain conditions the "incomplete" patients may be assumed to have a clinical course similar to the patients remaining under observation. This assumption is applied by multiplying the entries of columns (2)–(7) by the appropriate correction factor in column (11), thereby obtaining the expected percentages which are entered in columns (12)–(17). The expected percentages in the form of a broken line graph are presented in figure 3.

RESULTS

The clinical course of 448 cases of minimal pulmonary tuberculosis is presented graphically in figure 3. It is evident that the relative proportion (134/448) of patients having active disease at diagnosis is a specific instance of a fraction which in general may have any value between zero (no active cases) and one (all active cases). It is also evident (*see* figure 2) that the later admissions to study contain a greater proportion of patients with arrested disease than the earlier admissions. Hence, the data collected before the fourth anniversary are disproportionately influenced by the clinical course of the patients admitted with arrested disease, while the data collected after the fourth anniversary are disproportionately influenced by the clinical course of the patients admitted with active disease. Taking these circumstances into account, the following conclusions appear warranted:

1. Deaths from tuberculosis occur in the early anniversaries and continue throughout the ten years of observation.
2. The percentage of patients considered to have active disease decreases progressively throughout the first three years and then shows little change for the ensuing seven years.
3. Ten years after diagnosis a sizable proportion of the patients are lost and no longer available for follow-up examination. Losses to follow-up occur steadily throughout the study period.

The 448 patients were then divided into two subgroups consisting of: 314 patients classified as having arrested disease at the time of diagnosis and 134 patients classified as having active disease at diagnosis. The influence which the clinical status at diagnosis exerts on the after-history can readily be examined in these subgroups. In addition, the distortions caused by the admission of varying proportions of active and arrested cases are eliminated. The percentage of losses is unequal among the active and arrested cases (4 per cent and 10 per cent, respectively) and, since this inequality obscures comparisons between the two subgroups, consequently the losses will be disposed of by assuming that the untraced patients have an after-history similar to those who remain under observation. The appropriate calculations are indicated in tables 4 and 5.

The behavior of the 314 patients who were considered to have arrested disease at the time of diagnosis is shown in figure 4 and table 4. The essential points are:

TABLE 3

Patients with Minimal Tuberculosis Classified by Status at Each Anniversary

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
ANNIVERSARY	LIVING AT ANNIVERSARY			SINCE PREVIOUS ANNIVERSARY			TOTAL	INCOMPLETE	FACTORS		EXPECTED PERCENTAGES					
	Arrested	Presumably Arrested	Active	Died Tuberculosis	Died Nontuberculous Cause	Lost			Provisional	Correction	Arrested	Presumably Arrested	Active	Died Tuberculosis	Died Nontuberculous Cause	Lost
0	314	—	134	—	—	—	448	—	1.0000	0.2232	70.1	—	29.9	—	—	—
1	343	5	99	1	—	—	448	—	1.0000	0.2232	76.6	1.1	22.1	0.2	—	—
2	354	21	64	1	—	7	447	—	1.0000	0.2232	79.0	4.7	14.3	*0.2* 0.2	—	1.6
3	349	33	44	3	2	8	439	—	1.0000	0.2232	77.9	7.4	9.8	*0.4* 0.7	0.4	*1.6* 1.8
4	289	34	42	2	1	4	372	54	1.1452	0.2556	73.9	8.7	10.7	*1.1* 0.5	*0.4* 0.3	*3.4* 1.0
5	231	33	36	5	1	1	307	58	1.1889	0.3039	70.2	10.0	10.9	*1.6* 1.5	*0.7* 0.3	*4.4* 0.3
6	201	34	28	2	2	5	272	28	1.1029	0.3352	67.4	11.4	9.4	*3.1* 0.7	*1.0* 0.7	*4.7* 1.7
7	165	31	21	1	2	6	226	37	1.1637	0.3901	64.4	12.1	8.2	*3.8* 0.4	*1.7* 0.8	*6.4* 2.3
8	121	24	13	2	2	3	165	52	1.3152	0.5131	62.1	12.3	6.7	*4.2* 1.0	*2.5* 1.0	*8.7* 1.5
9	99	18	11	1	—	1	130	28	1.2154	0.6236	61.7	11.2	6.9	*5.2* 0.6	*3.5* —	*10.2* 0.6
10	78	12	8	2	3	—	103	25	1.2427	0.7749	60.4	9.3	6.2	*5.8* 1.6 *7.4*	*3.5* 2.3 *5.8*	*10.8* — *10.8*

(1) Number of years after diagnosis.
(2) Number of living patients with arrested disease at anniversary of diagnosis.

(3) Number of living patients with presumably arrested disease at anniversary.
(4) Number of living patients with active disease at anniversary.
(5) Number who died of tuberculosis since previous anniversary.
(6) Number who died of causes other than tuberculosis since previous anniversary.
(7) Number lost since previous anniversary.
(8) Total number at anniversary, sum of columns (2) to (7), inclusive.
(9) Number of "incomplete" patients at anniversary. These patients were alive and traced at the previous anniversary but had too short a follow-up to attain the specified anniversary.
(10) Provisional factor for anniversary $= \frac{\text{column (8)} + \text{column (9)}}{\text{column (8)}}$.
(11) Correction factor for anniversary = column (10) × correction factor for previous anniversary. The correction factor for anniversary 0 is 100/448 = 0.2232.
(12) Expected percentage of living patients with arrested disease at anniversary: column (2) × column (11).
(13) Expected percentage of patients with presumably arrested disease at anniversary: column (3) × column (11).
(14) Expected percentage of patients with active disease at anniversary: column (4) × column (11).
(15) Expected percentage of patients dead of tuberculosis at anniversary: column (5) × column (11). Cumulative percentages in italics.
(16) Expected percentage of patients dead of causes other than tuberculosis at anniversary: column (6) × column (11). Cumulative percentages in italics.
(17) Expected percentage of patients lost at anniversary: column (7) × column (11). Cumulative percentages in italics.

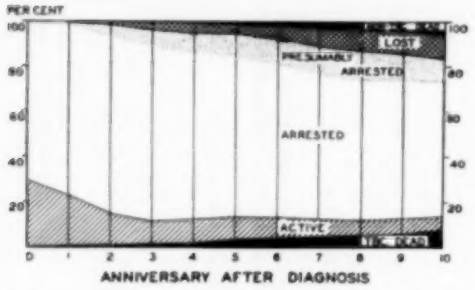

FIG. 3. Status at anniversary. Total minimal at diagnosis: 448 cases.

All active disease results from relapse.

Deaths from tuberculosis occur in the later years of observation.

Deaths from all causes, including tuberculosis, during the ten-year period (*see* table 4) amount to 19 and do not exceed the expected mortality, which is 25.6.

At the tenth anniversary approximately one-eighth of the patients have either died of tuberculosis or have active disease.

The after-history of the 134 patients who were considered to have active disease at the time of diagnosis is set forth in figure 5 and table 5. The points of interest are:

There is a rapid decrease in the percentage of active cases during the first three years, with little change thereafter.

Deaths from tuberculosis occur during the first year of observation and continue throughout. At each of the ten anniversaries the combined percentage of tuberculous deaths and cases with active disease never falls much below 20.

Deaths from tuberculosis during the ten-year period of observation (*see* table 5) amount to 14 and significantly exceed the expected mortality from all causes, which is 4.3.

From the third anniversary to the fifth, relapse accounts for an increasing proportion of patients who have active disease (*see* cross-hatched area of figure 5). A small percentage of the patients develop unremittingly active disease and survive to the end of the observation period.

Recently, doubt has once more arisen with respect to the efficacy of bed-rest treatment in minimal tuberculosis. Mitchell (4) was unable to find any relationship between the primary progression-relapse rate and the duration of modified bed rest, which varied between two and six months. In order to examine this question in the light of the data presented above, the 134 patients with active disease at diagnosis were divided into two groups:

Group A consisted of 62 patients who were hospitalized within three months of diagnosis and for an initial period of at least six months. Without exception, bed rest or modified bed rest was taken during this six-month period. *Group B* consisted of 72 patients who either were not hospitalized within three months

TABLE 4

PATIENTS WITH MINIMAL TUBERCULOSIS ARRESTED AT THE TIME OF DIAGNOSIS CLASSIFIED BY STATUS AT EACH ANNIVERSARY

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
ANNIVERSARY	LIVING AT ANNIVERSARY			SINCE PREVIOUS ANNIVERSARY		TOTAL	INCOMPLETE AND LOST	FACTORS		EXPECTED PERCENTAGES				
	Arrested	Presumably Arrested	Active	Died Tuberculosis	Died Nontuberculous Cause			Provisional	Correction	Arrested	Presumably Arrested	Active	Died Tuberculosis	Died Nontuberculous Cause
0	314	—	—	—	—	314	—	1.0000	0.3185	100.0	—	—	—	—
1	308	3	3	—	—	314	—	1.0000	0.3185	98.1	0.9	0.9	—	—
2	280	18	9	—	—	307	7	1.0228	0.3257	91.2	5.9	2.9	—	—
3	258	29	12	—	2	301	6	1.0199	0.3322	85.7	9.6	4.0	—	0.7
														0.7
4	207	28	18	—	1	254	45	1.1772	0.3911	81.0	11.0	7.0	—	0.4
														1.1
5	160	27	12	3	1	203	50	1.2463	0.4874	78.0	13.2	5.8	1.4	0.5
													1.4	*1.6*
6	131	29	12	1	2	175	24	1.1371	0.5542	72.6	16.1	6.7	0.6	1.1
													2.0	*2.7*
7	105	24	9	—	2	140	32	1.2286	0.6809	71.5	16.3	6.1	—	1.4
													2.0	*4.1*
8	67	17	7	1	2	94	44	1.4681	0.9996	67.0	17.0	7.0	1.0	2.0
													3.0	*6.1*
9	52	14	6	—	—	72	19	1.2639	1.2634	65.7	17.7	7.6	—	—
													3.0	*6.1*
10	38	9	5	1	3	56	16	1.2857	1.6244	61.7	14.6	8.1	1.6	4.9
													4.6	*11.0*

TABLE 5

PATIENTS WITH MINIMAL TUBERCULOSIS ACTIVE AT THE TIME OF DIAGNOSIS CLASSIFIED BY STATUS AT EACH ANNIVERSARY

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
ANNIVERSARY	LIVING AT ANNIVERSARY				SINCE PREVIOUS ANNIVERSARY DIED TUBERCULOSIS	TOTAL	INCOMPLETE AND LOST	FACTORS		EXPECTED PERCENTAGES				
	Arrested	Presumably Arrested	Active, Never Arrested	Active by Relapse				Provisional	Correction	Arrested	Presumably Arrested	Active, Never Arrested	Active by Relapse	Died Tuberculosis
0	—	—	134	—	—	134	—	1.0000	0.7463	—	—	100.0	—	—
1	35	2	96	—	1	134	—	1.0000	0.7463	26.1	1.5	71.6	—	0.7
														0.7
2	74	3	55	—	1	133	—	1.0000	0.7463	55.2	2.2	41.1	—	0.7
														1.4
3	91	4	30	2	3	130	2	1.0154	0.7578	69.0	3.0	22.7	1.5	2.3
														3.7
4	82	6	17	7	2	114	13	1.1140	0.8442	69.2	5.1	14.4	5.9	1.7
														5.4
5	71	6	13	11	2	103	9	1.0874	0.9180	65.2	5.5	11.9	10.1	1.8
														7.2
6	70	5	8	8	1	92	9	1.0978	1.0078	70.6	5.0	8.1	8.1	1.0
														8.2
7	60	7	5	7	1	80	11	1.1375	1.1464	68.8	8.0	5.7	8.0	1.2
														9.4
8	54	7	3	3	1	68	11	1.1618	1.3319	71.9	9.3	4.0	4.0	1.3
														10.7
9	47	4	3	2	1	57	10	1.1754	1.5655	73.6	6.3	4.7	3.1	1.6
														12.2
10	40	3	2	1	1	47	9	1.1915	1.8653	74.6	5.6	3.7	1.9	1.9
														14.1

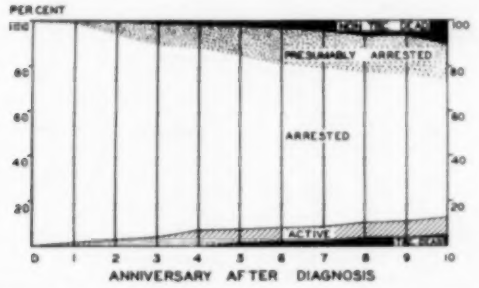

FIG. 4. Status at anniversary. Minimal arrested at diagnosis: 314 cases.

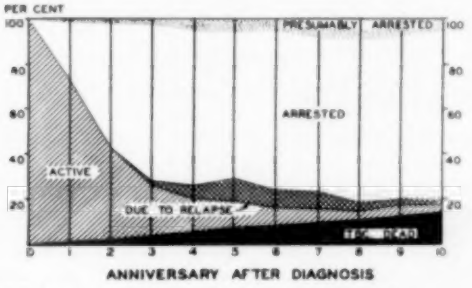

FIG. 5. Status at anniversary. Minimal active at diagnosis: 134 cases.

of diagnosis or failed to remain in the hospital for an initial period of six months.

In *Group A* the median length of the waiting period between diagnosis and hospitalization was 3 weeks and the median length of hospital stay was 18.5 months. On the other hand, *Group B* included 19 persons who were not hospitalized at all. The median delay in hospitalization among the remaining 53 patients was 11 months and the median length of hospital stay was 9 months. There were no significant differences either in the age distributions or in the proportion of males and females observed in the two groups. The clinical course of the two groups of patients is compared in figure 6.

There are several possible explanations for the lack of any striking difference in the clinical course of the two groups. First, the method of analysis employed is not sufficiently sensitive to detect a small but significant difference which may exist. Second, the criteria according to which the two groups were chosen have given rise to a biased selection of patients, i.e., the clinical material included in the two groups is not really comparable. For example, the patients in *Group B* may have delayed or refused hospitalization because they did not experience the distressing symptoms which commonly accompany progressive tuberculosis. Again, hospitalization may not have been recommended so frequently in *Group B* because the disease was thought to be of an indolent nature.

In the opinion of the writers, the data shown in figure 6 should not be interpreted as disproving the value of bed rest. Additional factors, such as those

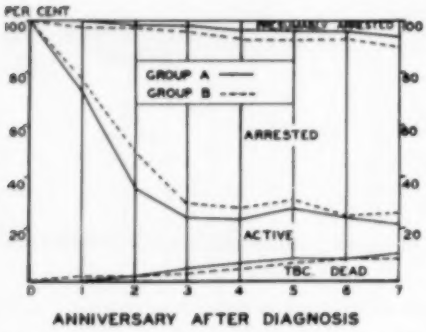

FIG. 6. Comparison of clinical course: *Group A*—62 patients; *Group B*—72 patients.

TABLE 6

RELAPSE RATES* AMONG PATIENTS WITH MINIMAL TUBERCULOSIS AT TIME OF DIAGNOSIS

Number of years of observation	2	3	4	5	6	7	8	9	10
Number of patients with arrested disease at beginning of year	392	346	275	215	173	136	95	70	37
Number of relapses during year	15	10	7	3	1	0	0	0	0
Relapse rate (in per cent)	3.8	2.9	2.5	1.4	0.6	0	0	0	0

* In calculating these rates, only initial relapses are considered. Observation periods of one year or less in length are omitted because of the inherent lack of precision in dating the event "relapse of disease" (*see* (1)).

noted above, may explain the comparable clinical course of the two groups of patients. More study of the efficacy of bed rest is needed, preferably to include a larger number of patients placed on one of several regimens according to a predetermined plan.

Thus far, attention has been directed to the percentages of patients who have arrested disease, or active disease, or who are dead at various anniversaries of diagnosis. It is of some interest to determine the rates at which patients are being exchanged among the various categories and to assess the influence exerted on these rates by the passage of time.

The relapse rate among patients who were under observation for a stated number of years is shown in table 6. The relapse rate for, say, the sixth year of observation is obtained by dividing the number of persons whose disease remains arrested for five years and who experience relapse in the sixth year by the number whose disease remains arrested at least five years and who are observed throughout the succeeding year. The table includes only relapses which could be dated with reasonable accuracy.[3] The data in the table suggest that the relapse rate declines as the number of years of observed uninterrupted arrest

[3] Of the 12 relapses which could not be accurately dated, 11 occurred during the first five years of observed arrest and one occurred after more than five years of arrest.

TABLE 7

REMISSION RATES* AMONG PATIENTS WITH MINIMAL TUBERCULOSIS AT TIME OF DIAGNOSIS

Number of years of observation	2	3	4	5	6	7
Number of patients with active disease at beginning of year	118	71	37	23	16	10
Number of remissions during year	45	26	9	3	3	1
Remission rate (in per cent)	38.1	36.6	24.3	13.0	18.7	10.0

* In calculating these rates, only initial remissions are considered. Observation periods of one year or less in length are omitted because of the inherent lack of precision in dating the event "arrest of disease" (*see* (1)).

increases. As the actual length of arrested disease may exceed the observed length as shown in table 5, the relapse rates should be regarded as minimum estimates. A total of 48 persons had at least one relapse during the study period. Of the 48 initial relapses, 39 were characterized by sputum positive for tubercle bacilli, accompanied by an increase in the roentgenographic shadows; while the remaining 9 represented roentgenographic progression unaccompanied by "positive" sputum.

The rate at which remission (arrest of disease) occurred among patients who were under observation for a stated number of years is set forth in table 7. The remission rate for, say, the fifth year of observation is obtained by dividing the number of persons whose disease is continuously active for four years and who attain the arrested status in the fifth year by the number of persons whose disease is active for at least four years and who are observed throughout the succeeding year. The data in the table indicate that the remission rate declines as the number of years of observed uninterrupted active disease increases.

DISCUSSION

In a necropsy study of cases of sudden death, Medlar (5) observed that tuberculous lesions of sufficient size to be evident on the chest roentgenogram always contain an area of necrosis. At the present time, the belief is widely held that liquefaction of the necrotic lesion and its dispersion through the airways cause extension of the tuberculous process. Thus, when a person with active minimal disease has a "spread," it is because a necrotic area has disintegrated relatively early after its formation. Similarly, when a person with arrested disease experiences a relapse, the necrotic focus has undergone a delayed disintegration and extension.

It is clear that an indispensable requirement for relapse is the presence of virulent tubercle bacilli in the necrotic lesion which undergoes disintegration. A number of investigators, using either animal inoculation or cultural techniques, have found that the likelihood of demonstrating viable organisms decreases as the apparent age of the necrotic lesion increases. Sweany (6) was able to obtain positive cultures from only 10 of 286 calcified caseous (necrotic) lesions which, in his estimation, were more than ten years old. Canetti (7), on the basis of his

own studies and a careful review of the literature, concludes that caseous lesions approximately five years of age are positive by animal inoculation or on culture in 20 per cent of the cases.

It is of some interest that the decrease in the relapse rate during the early years of observation (*see* table 6) is not inconsistent with the findings of Canetti and of Sweany, i.e., the longer the necrotic lesion remains intact, the smaller the probability of its containing viable organisms; hence, the less hazard of relapse. In addition, the observed decline in the relapse rate may reflect a decreasing tendency of the necrotic lesion to undergo dissolution. Bobrowitz (2), Reisner (8), and Mitchell (9) have likewise observed a steady decrease in the relapse rate in minimal tuberculosis during the first five years of observed arrest. It is not a hard and fast rule, however, that, in minimal tuberculosis, relapse is impossible after five years of proved clinical arrest for, as every clinician knows, there are occasional exceptions. Recently the present writers have seen relapse occur in a patient with minimal disease who had had stable yearly chest roentgenograms over a period of thirteen years.

The remission rates in table 7 show a marked and steady decline as the years of unremitting disease increase. It is the writers' belief that the establishment of advanced disease with open cavity becomes more and more likely as the duration of active tuberculosis increases.

The implications of the data in tables 6 and 7 provide an important clue to the changing proportions of patients who have either arrested or active disease, or who are dead (*see* figures 4 and 5). For example, the initially rapid decrease in the proportion of active cases shown in figure 5 is related to the high remission rate that is observed during the early years after diagnosis. As a result of these remissions, a substantial number of patients with arrested disease is accumulated. However, since these patients have *newly* arrested disease, the relapse rate is high and, at the fourth anniversary, an increasing number of relapses is seen. Hereafter, the exchange between the various categories slows down, the patients with arrested disease tending to remain well and those with active disease tending to remain ill.

The influence of decreasing relapse and remission rates on a group of patients who have arrested disease at diagnosis is demonstrated in figure 4. Relapses occur during the first several anniversaries, resulting in a small number of cases of active disease. Some remissions occur at the earlier anniversaries but by the sixth year after diagnosis a rather static situation is observed; a small proportion of patients have developed chronic disease but the great majority have arrested disease. During the later anniversaries an occasional relapse and a sporadic death occur.

What are the clinical implications of the results discussed above? The most important, perhaps, is that no one should be complacent about minimal tuberculosis. During the years 1937–1947, when the patients in the present report were discovered to have tuberculosis, chemotherapy was not in general use. Minimal disease which was active at the time of diagnosis could be expected to cause death or continuing disability in fully one-fifth of the patients. Minimal

disease which was arrested at the time of diagnosis could be expected to cause death or disability in fully one-eighth of the patients. The fact that relapse appears to be relatively less frequent as the number of years of arrest increases is more than offset by the fact that the chances of remission decrease as the duration of unremittingly active disease increases. Unremittingly active tuberculosis frequently results in death but it may also result in the so-called "good chronic" status (10). At the present time it appears that the person with undiagnosed chronically active disease plays an important, if not the principal, role in spreading pulmonary tuberculosis (11).

SUMMARY

During the years 1937–1947, 448 residents of the hospital district were found to have minimal pulmonary tuberculosis, the disease being classified as arrested in 314 of them and as active in 134. There was an increase in the annual incidence of new cases of arrested minimal tuberculosis, but no change in the annual incidence of new cases of active minimal tuberculosis. Finally, the median age of the patient at the time of diagnosis rose significantly.

Analysis of the follow-up data showed that:

1. One-fifth of the persons who had active disease at the time of diagnosis could be expected either to be dead of tuberculosis or to have active disease ten years later.
2. One-eighth of the persons who had arrested disease at the time of diagnosis could be expected either to be dead of tuberculosis or to have active disease ten years later.
3. There was a steady decline in the relapse rate as the duration of arrest of disease increased.
4. There was a similar decline in the remission rate as the duration of active disease increased.

There was a strong tendency for cases of newly diagnosed, active minimal tuberculosis to become arrested (high remission rate) and a moderate tendency for cases of newly arrested disease to become active again (moderate relapse rate). The weakening of these tendencies with the passage of time is consistent with certain pathologic and bacteriologic aspects of the necrotic lesion.

SUMARIO

La Historia Subsecuente de la Tuberculosis Pulmonar: III Tuberculosis Mínima

Durante los años 1937–1947, se descubrió que 448 residentes de un distrito hospitalario tenían tuberculosis pulmonar mínima, clasificándose ésta como estacionada en 314 y como activa en 134. Observóse un aumento en la incidencia anual de nuevos casos de tuberculosis mínima estacionada, pero no hubo cambio en la de nuevos casos de la forma mínima activa. Por fin, la edad media de los enfermos en la fecha del diagnóstico se elevó notablemente.

En análisis de los datos aportados por la observación subsiguiente reveló que:

1. Cabía esperar que la quinta parte de las personas que tenían afección activa al hacerse el diagnóstico bien hubieran muerto de tuberculosis o tuviesen enfermedad activa diez años después.
2. Cabía esperar que la octava parte de las personas que tenían afección esta-

cionada al hacerse el diagnóstico bien hubieran muerto de tuberculosis o tuviesen enfermedad activa diez años después.

3. Había una baja constante en la tasa de recidivas a medida que aumentaba la duración del estacionamiento de la dolencia.

4. Había una baja semejante en la tasa de remisiones a medida que aumentaba la duración de la enfermedad activa.

Observóse una poderosa tendencia al estacionamiento (tasa elevada de remisiones) de parte de los casos de tuberculosis mínima activa recién diagnosticada y una tendencia moderada a la activación (tasa moderada de remisiones) de parte de los casos de enfermedad recién estacionada. La atenuación de esas tendencias con el transcurso del tiempo resulta compatible con ciertos aspectos histopatológicos y bacteriológicos de la lesión necrótica.

RESUME

Historique des suites de la tuberculose pulmonaire: III Tuberculose a minima

Au cours des années 1937–1947, la tuberculose pulmonaire avec lésions minimales a été découverte chez 448 individus hospitalisés dans l'hôpital régional, la maladie étant classifiée comme stabilisée chez 314 d'entre eux et active chez 134. L'incidence annuelle de nouveaux cas de tuberculose *a minima* stabilisée a subi un accroissement, mais il n'y a eu aucun changement en ce qui concerne l'incidence annuelle de nouveaux cas de tuberculose *a minima* active. Enfin, l'âge moyen du malade au moment du diagnostic s'est élevé d'une façon significative.

L'analyse des données fournies par la surveillance ultérieure des malades a indiqué que:

1. Pour un cinquième des sujets atteints de tuberculose en activité au moment du diagnostic on pouvait prévoir soit le décès par tuberculose soit une tuberculose en activité dix ans plustard.

2. Pour un huitième des sujets présentant une tuberculose stabilisée au moment du diagnostic on pouvait prévoir soit la mort par tuberculose soit une tuberculose en activité dix ans plus tard.

3. Le taux des rechutes diminuait régulièrement à mesure que la durée de la stabilisation de la maladie augmentait.

4. Une diminution similaire du taux de rémission s'observait à mesure que la durée de l'activité de la maladie augmentait.

Il existait une tendance marquée à la stabilisation (taux de rémission élevé) pour les cas de tuberculose a minima active récemment diagnostiqués et une tendance modérée pour les cas récemment stabilisés à redevenir actifs (taux de rechute modéré). L'affaiblissement de ces tendances avec le temps s'accorde avec certains aspects pathologiques et bactériologiques de la lésion nécrotique.

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TUBERCULOSIS MORBIDITY AND MORTALITY AMONG MENTAL PATIENTS AS COMPARED WITH THE GENERAL POPULATION[1]

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INTRODUCTION

The greater frequency of tuberculosis as a cause of illness and death among mental patients as compared with the general population has been known for a long time and has been considered by some to be due to constitutional factors which render patients with mental diseases more susceptible to tuberculosis. That constitutional factors are involved in the development of tuberculosis has been shown by the animal experiments of Lurie (1) and the twin studies of Kallmann and Reisner (2). These writers also admit the importance of environmental factors, but their studies provide no indication of the relative importance of each in the development of the disease among humans. The question, therefore, is not whether constitutional factors are involved, but rather whether they are of greater importance among mental patients than among the mentally well.

As far as mental patients are concerned, the importance of determining the true explanation lies in the course of action necessitated by the acceptance of a greater constitutional lack of resistance as the major factor in the development of tuberculosis. Such an explanation implies that, in order to protect those with a greater hereditary susceptibility, the methods ordinarily applicable in the control of tuberculosis—early diagnosis, segregation, and treatment—may have to be intensified to an impracticable degree. As an example, if mental patients have a significantly lower constitutional resistance to tuberculosis, biennial or annual roentgenographic examinations may be considered much too infrequent to reduce the period of exposure to unrecognized infectious tuberculosis, and even semi-annual examinations may not reduce exposure enough to prevent considerable spread of the disease among the patients within the institutions. Moreover, other extraordinary procedures not practicable in large institutions, such as extremely long periods of segregation of all tuberculous patients, may be necessary to shield nontuberculous inmates from possible exposure to infectious tuberculosis. Furthermore, treatment of the tuberculosis of constitutionally less resistant patients may be expected to be less effective than if there were no such innate lack of resistance. On the other hand, if the development of tuberculosis by mental patients is basically similar in origin to that of the general population, similar results may be expected among the mentally ill to those obtained from the tuberculosis control methods now being applied to the population as a whole.

It is the purpose of the present report to study the available data in an effort to determine whether the higher tuberculosis morbidity and mortality among the mentally ill may be explained on epidemiologic grounds other than constitu-

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tional, within the concept of tuberculosis as an infectious disease. The study is based upon the assumption that, if the differences in tuberculosis morbidity and mortality rates between mental patients and the general population can be explained by the characteristics of the disease, such as differences in distribution in age and conditions of exposure, there is no need to assume any differences in resistance to tuberculosis between the two groups on a hereditary basis.

MATERIALS AND METHODS

The data presented were obtained during the course of a tuberculosis control program conducted jointly since 1941 by the New York State Departments of Health and of Mental Hygiene among the 90,000 patients in the 20 hospitals of the latter department. This program includes chest roentgenograms of all patients on admission, periodic chest roentgenographic surveys of patients in all institutions, and segregation and treatment of tuberculous patients. The term *clinically significant* is used for cases of pulmonary tuberculosis classified as *active*, *quiescent*, *apparently arrested*, or *arrested* in the 1940 edition of *Diagnostic Standards* published by the National Tuberculosis Association or as *active* or *arrested* in the 1950 edition. Cases classified as *apparently cured* in the 1940 edition or as *inactive* in the 1950 edition are considered *not clinically significant*. Because of the nature of the material, it was found more practical to consider details under the various headings in the discussion.

OBSERVATIONS

In comparing the tuberculosis morbidity and mortality among mental patients and the general population of New York State, certain basic differences between the two groups must be recognized and their importance considered in any conclusions drawn. The differences include the following factors:

Morbidity data are more nearly complete and more accurate for mental patients. All mental patients have chest roentgenograms upon admission to institutions and periodically thereafter, so that the presence or absence of pulmonary disease is known. In the general population, on the other hand, chest roentgenographic examinations are made infrequently so that, for the population as a whole, much of the essential basic data regarding the prevalence and incidence of tuberculosis are not available. As a result, statements regarding tuberculosis morbidity among mental patients have a much better basis in factual data than those for the general population.

There is a marked difference in the age distribution of patients in mental hospitals as compared with the rest of the State's population. Thus, the average age of patients in mental hospitals is about fifty-three years (3), while that of the general population is about thirty-four. This difference is of great importance because of the correlation between age and morbidity and mortality from tuberculosis.

Because of the higher average age of mental patients and because of factors associated with their mental disease, patients in mental hospitals have more physical disease, other than tuberculosis, than the general population.

There are marked differences in environment. The effect of hospitalization of patients with mental disease, with resulting overcrowding and increased opportunity for exposure to infectious tuberculosis, must be considered. To this should be added the possible effects of poor personal hygiene and poor feeding habits of some patients.

TABLE 1

PREVALENCE OF CLINICALLY SIGNIFICANT* PULMONARY TUBERCULOSIS AMONG PATIENTS ADMITTED OR READMITTED TO MENTAL HOSPITALS 1949–1951, UPSTATE NEW YORK AND NEW YORK STATE

AREA AND SEX	TOTAL			YEAR OF ADMISSION OR READMISSION								
				1949			1950			1951		
	Number	Cases of Tuberculosis	Rate	Number	Cases of Tuberculosis	Rate	Number	Cases of Tuberculosis	Rate	Number	Cases of Tuberculosis	Rate
			per cent			*per cent*			*per cent*			*per cent*
Upstate†												
Both Sexes	25,542	309	1.2	8,657	99	1.1	8,416	98	1.2	8,469	112	1.3
Males	12,833	201	1.6	4,366	63	1.4	4,210	67	1.6	4,257	71	1.7
Females	12,709	108	0.8	4,291	36	0.8	4,206	31	0.7	4,212	41	1.0
New York State												
Both Sexes	62,734	1,101	1.8	21,260	342	1.6	20,674	389	1.9	20,800	370	1.8
Males	30,900	754	2.4	10,512	229	2.2	10,138	279	2.8	10,250	246	2.4
Females	31,834	347	1.1	10,748	113	1.1	10,536	110	1.0	10,550	124	1.2

* Clinically significant: cases of pulmonary tuberculosis classified as *active*, *quiescent*, *apparently arrested*, or *arrested* in the 1940 edition of *Diagnostic Standards*, published by the National Tuberculosis Association, or as *active* or *arrested* in the 1950 edition.

† New York State, exclusive of New York City.

As a result of these limitations of the available data and the differences between the two groups, the present report cannot make a precise numerical comparison of the real tuberculosis morbidity and mortality among mental patients and the general population. It is, rather, an attempt to piece together a sufficient number of small bits of information, each of which by itself may be of slight importance, but which in summation will be sufficient to show with some degree of clarity a good, though incomplete, view of the epidemiology of tuberculosis among mental patients.

The prevalence of tuberculosis among patients upon admission to mental hospitals will be considered first, followed by study of the incidence, mortality, and prevalence among patients after admission.

Prevalence of Tuberculosis Among Patients on Admission to Mental Hospitals

Chest roentgenographic examinations made at the time of admission or readmission of patients to mental hospitals in Upstate New York (New York State exclusive of New York City) from 1949 through 1951 revealed *clinically significant* tuberculosis in 1.2 per cent of all patients (table 1).

There is no accurate information available regarding the prevalence of *clinically significant* tuberculosis in the adult population of the upstate area, but from such data as are available it is estimated at approximately 0.55 per cent. This figure is obtained as follows:

The rate obtained in mass surveys was applied to the upstate population (more than fifteen years of age), excluding those admitted to general hospitals. To

the latter portion of the population the rates found among general hospital admissions were applied. The number of cases thus estimated in these two segments of the population, comprising the unknown cases, added to the known cases on the tuberculosis case registers of the various cities and counties in Upstate New York constitute the total number of cases present in the general population. This calculation produces an estimate of 28,857 cases, and a prevalence of 0.55 per cent.

The value obtained is believed to be an underestimate, since the mass surveys are held predominantly in rural and smaller population areas where the rates are known to be lower. Moreover, there is a widespread feeling that the groups most likely to profit from surveys are least likely to appear for examination. The data used in this table refer only to the upstate area rather than to the entire State, including New York City. Information is available only for upstate of the prevalence of tuberculosis by age and sex among persons examined in community surveys and general hospital admissions for a similar time period (1949–1951) to that for the mental hospital admissions studied here. Moreover, recent data from the tuberculosis case registers are available for the upstate area. Neither of these sets of data is available for New York City, but conclusions based upon Upstate New York data are probably applicable to the State as a whole.

If the rate of 0.55 per cent is used, then there is twice as much tuberculosis among mental patients on admission to mental hospitals as in the general upstate population. This excessive amount of tuberculosis among mental patients might at first glance be interpreted as evidence in favor of a constitutional inferiority which makes them more susceptible to tuberculosis, as the disease is diagnosed upon admission, before the adverse environmental factors associated with hospitalization (such as overcrowding and exposure to unrecognized cases of tuberculosis) have had an opportunity to exert their effect. There are several factors, however, which explain, in part at least, the difference in tuberculosis prevalence between the two groups:

Differences in age distribution explain part of the discrepancy. Mental patients are considerably older than those examined in mass surveys, or those admitted to general hospitals, or the population of the State as a whole. When the age distribution of the general population is adjusted so that it is similar to that of mental hospital admissions, there is a relative increase of approximately 25 per cent in the prevalence of tuberculosis in the general population, from 0.55 per cent to 0.69 per cent.

Patients admitted to mental hospitals are, to a considerable extent, drawn from those population groups among which the prevelance of tuberculosis is high so that, in general, those areas of the State which have high rates of reported cases of tuberculosis also have high mental hospital admission rates. A close correlation throughout the State between the tuberculosis case rates per 100,000 population and the mental hospital admission rates are shown in columns 3 and 6 of table 2. This need not necessarily be interpreted to mean that there is a cause and effect relationship between mental disease and tuberculosis, but simply that there are factors common to both types of disease. If an allowance is made for the correlation between tuberculosis case reports and admission rates from the various population centers of the State, the prevalence among admissions to mental hospitals may be expected to be greater by approximately 17 per cent, and perhaps more.

TABLE 2

TUBERCULOSIS CASE REPORT RATES AND RATES OF FIRST ADMISSIONS TO MENTAL HOSPITALS FOR CERTAIN SUBDIVISIONS OF NEW YORK CITY AND UPSTATE, AND CORRELATION BETWEEN TUBERCULOSIS RATES AND ADMISSION RATES 1946–1950

	TUBERCULOSIS CASES REPORTED*			MENTAL ADMISSIONS†		
	Number (1)	Rate per 100,000 (2)	Rank (3)	Number (4)	Rate per 100,000 (5)	Rank (6)
New York City						
Manhattan	18,966	193.0	1	17,857	181.7	1
Bronx	5,122	70.4	9	5,838	80.2	9
Brooklyn	10,087	73.5	8	13,930	101.5	5
Queens	4,609	59.3	10	4,948	63.6	11
Richmond	528	55.0	12	710	73.9	10
Upstate						
Buffalo	4,533	152.6	2	2,924	98.4	6
Rochester	1,269	76.2	6	2,050	123.2	3
Other places over 100,000	2,261	89.5	3	3,138	124.0	2
Places 25,000–100,000	3,597	76.2	7	4,308	91.2	8
Places 10,000–25,000	3,502	82.5	5	3,876	93.6	7
Places 2,500–10,000	2,893	84.2	4	3,545	103.1	4
Rural	7,252	56.0	11	8,085	62.5	12

The rank correlation is 0.84. The standard error is 0.30. The probability that this is due to chance is less than 0.01.

* Upstate reported cases from annual reports of New York State Department of Health, Office of Vital Statistics. New York City reported cases from 1952 report of New York Tuberculosis and Health Association.

† Data for mental hospital admissions from annual reports of New York State Department of Mental Hygiene.

These calculations are based on case rates because prevalence rates by area were not available. Since prevalence, incidence, and mortality are related, the relative effect should be similar regardless of which index is used. The manner in which the effect of the correlation was calculated is shown in table 3.

Essentially, two calculations are made: One assumes correlation and one does not. Column 1 in table 3 shows the actual number of admissions to the mental hospitals from twelve subdivisions of the State. Column 2 shows the same total distributed in proportion to the general population of these areas; this assumes that the admission rate was the same in these twelve areas. Column 3 shows the tuberculosis case rates for these subdivisions of the State.

Columns 4 and 5 show the tuberculosis rates in column 3 applied to columns 1 and 2. This shows that the number of cases among admissions is much higher in column 4 (where correlation exists) than in column 5 in those areas where tuberculosis rates are high; the number is *less* in areas with low tuberculosis rates. The increase in the high tuberculosis areas, however, exceeds the decrease in the low tuberculosis areas, so that there is a greater number of cases for the State as a whole when computed on basis of correlation. The ratio of the number obtained on the basis of correlation to that without correlation shows to what extent prevalence among mental admissions should exceed that of the general

TABLE 3

ACTUAL NUMBER OF FIRST ADMISSIONS AND ESTIMATED NUMBER (BASED ON ABSENCE OF CORRELATION BETWEEN ADMISSION AND TUBERCULOSIS RATES); REPORTED CASE RATES (USED AS AN INDEX OF PREVALENCE OF TUBERCULOSIS) IN THE SUBDIVISIONS OF NEW YORK STATE AND ESTIMATES OF THE NUMBER OF TUBERCULOSIS CASES AMONG ADMISSIONS BASED ON THE PRESENCE AND ABSENCE OF CORRELATION, 1946–1950

	FIRST ADMISSIONS (1946–1950)		REPORTED TUBERCULOSIS CASE RATE (PER 100,000 POPULATION)	RELATIVE NUMBER OF TUBERCULOSIS CASES EXPECTED AMONG ADMISSIONS ON BASIS OF:	
	Actual Number (Positive Correlation) (1)	Number Expected on Basis of Population (No Correlation) (2)	(3)	Case Rates × Actual Admissions (Correlation) (4)	Case Rates × Estimated Admissions (No Correlation) (5)
New York State	71,209	71,209	89.7		
New York City	43,283	39,091	99.4	43.02	38.86
Manhattan	17,857	9,709	193.0	34.46	18.74
Brooklyn	13,930	13,563	73.5	10.24	9.97
Bronx	5,838	7,181	70.4	4.11	5.06
Queens	4,948	7,682	59.3	2.93	4.56
Richmond	710	948	55.0	0.39	0.52
Upstate					
Buffalo	2,924	2,934	152.6	4.46	4.48
Rochester	2,050	1,645	76.2	1.56	1.25
Places of					
100,000–250,000	3,138	2,497	89.5	2.81	2.23
25,000–100,000	4,308	4,666	76.2	3.28	3.56
10,000–25,000	3,876	4,196	82.5	3.20	3.46
2,500–10,000	3,545	3,396	84.2	2.98	2.86
Rural	8,085	12,784	56.0	4.53	7.16
New York State total				74.95	63.87

population *on the basis of this factor alone*. The number based on correlation is 74.95, while that based on lack of correlation is 63.87; the former is 17.3 per cent greater than the latter.

Since the subdivision of the State into twelve areas is crude, it appears that, were data for mental hospital admission rates available for smaller subdivisions as they are for tuberculosis case rates, a much greater percentage of the difference between the prevalence of tuberculosis in the general population and that of admissions to the mental hospitals would be accounted for.

Faris and Dunham (4) found that, in the city of Chicago, "high insanity rates appear to cluster in the deteriorated regions in and around the center of the city, no matter what race or nationality inhabits that region." Since it is well known that such areas have high tuberculosis rates, this constitutes supporting evidence of the geographic relationship between the prevalence of mental disease and tuberculosis.

In addition to age and economic status, the presence of nontuberculous organic disease and its effect upon the prevalence of tuberculosis must be con-

sidered. At the time of admission these patients suffer to a considerable extent from other diseases (5). Although the extent of morbidity from all diseases in the general population is not known, it is presumably much less than among mental patients. It seems quite reasonable to assume that the presence of these other diseases may reduce patients' resistance to tuberculosis, even though the relationship between the two cannot be stated quantitatively.

In this attempt to explain the reason for the differences in the tuberculosis prevalence rate among patients on admission to mental hospitals and the general adult population, it must be emphasized that the individual figures used in making the comparisons are not to be taken too literally. Rather, they are used to demonstrate that there are factors of epidemiologic importance which show *why* differences in prevalence must be expected, even though the quantitative extent of these differences cannot be entirely explained. They show that the significance of the difference in prevalence in the two groups is considerably less than the gross figures indicate.

Incidence of Tuberculosis Among Patients Within Mental Hospitals

As the study of the incidence of tuberculosis is concerned with the rate of development of new cases, only those patients whose roentgenograms show evidence of tuberculosis following one or more previously negative films are included in this portion of the report. All of the twenty mental hospitals of the Department of Mental Hygiene have had three chest roentgenographic surveys, while fifteen have had four. In order to have as long a period of observation as possible, only those with four surveys are considered. Conclusions based upon the findings in these fifteen hospitals are considered valid for all because the incidence rates obtained in them up through the time of the third survey were quite similar to those for the entire group.

In comparing the incidence of tuberculosis among mental patients with that for the general population, the interval between 1941 and 1952 is considered separately for three periods. During the period between the first and second surveys, 1941–1944, the average tuberculosis incidence was 5.6 per 1,000 person-years. In the period between 1945 and 1948 (period between second and third surveys), the rate decreased to 3.2 per 1,000 person-years; and between 1949–1952 (third to fourth surveys), there was a further decrease to 2.2 (table 4.4). Thus, using the incidence rate obtained in the time between the first and second surveys as a basis for comparison, there was a decrease of 43 per cent during the interval between the second and third, and 32 per cent between the third and fourth surveys. For the entire period the decrease was 61 per cent.

In attempting a comparison of the incidence among mental patients with that in the general population, the same obstacle is met as when prevalence rates were considered—absence of reliable data for the State as a whole. However, in order to obtain some figures as a basis for comparison, even though they may be only an approximation of the actual rates, the tuberculosis cases reported per 100,000 population of Upstate New York for the period between 1941 through 1952 may be used as an index of the rate of development of tubercu-

TABLE 4

COMPARISON OF INCIDENCE OF PULMONARY TUBERCULOSIS AMONG MENTAL PATIENTS AND TUBERCULOSIS CASE RATES FOR NEW YORK STATE 1941–1952

A. Incidence of Pulmonary Tuberculosis in Mental Hospitals

AGE	FIRST–SECOND SURVEY		SECOND–THIRD SURVEY		THIRD–FOURTH SURVEY	
	Cases of Tuberculosis Developed	Rate per 1,000 Person-Years	Cases of Tuberculosis Developed	Rate per 1,000 Person-Years	Cases of Tuberculosis Developed	Rate per 1,000 Person-Years
All ages	1,081	5.6	595	3.2	303	2.2
Less than 25	55	7.5	25	3.8	11	2.2
25–44	486	8.5	219	4.2	97	2.7
45–64	411	4.9	240	3.0	138	2.4
65 and older	129	2.9	111	2.3	57	1.4
Per cent decrease from previous period				43.2		31.9
Per cent decrease from first period						61.3

B. Tuberculosis (Respiratory) Case Rates, New York State 1941–1952

AGE	1941–1944		1945–1948		1949–1952	
	Cases of Tuberculosis Reported	Rate per 1,000 Population	Cases of Tuberculosis Reported	Rate per 1,000 Population	Cases of Tuberculosis Reported	Rate per 1,000 Population
All ages	54,562	0.99	46,656	0.82	45,166	0.75
Less than 25	11,618	0.58	10,560	0.52	9,972	0.46
25–44	22,839	1.23	17,045	0.90	16,199	0.85
45–64	15,477	1.23	14,452	1.08	13,887	0.97
65 and older	4,628	1.13	4,599	1.00	5,108	1.00
Ages adjusted to mental hospital population		1.19		0.99		0.92
Per cent decrease from previous period				17.1		6.2
Per cent decrease from first period						22.2

losis in the State. Admittedly, not all cases of tuberculosis are reported, and not all cases reported in any given year are developed during that year. Nevertheless, if case-finding activities remained at about the same level during the period, the ratio of cases reported to the adult population might be used as an approximation of the incidence rate and, perhaps somewhat more accurately, as an indication of the *trend* of incidence during this time period.

Based upon this assumption, table 4*B* shows average incidence rates for the New York State population for the three time periods. When the age distribution is adjusted to that of patients in mental hospitals, the rates are about 1.2, 1.0, and 0.9, respectively. Between the first and second periods, the incidence decreased 17 per cent; between the second and third, 6 per cent; while for the entire time, the decrease was 22 per cent. As shown in table 4 (*A* and *B*), the

incidence rate among mental patients, which was about five times that of the general population during the first period, was less than 2.5 times as high by the time of the third period. Thus, it is obvious that, while tuberculosis develops at a higher rate among mental patients than in the general population, the differences in rates are becoming smaller.

The causes of the decreasing incidence in the general population are multiple and difficult to determine, although those factors usually included in the term "improved standards of living" are of considerable importance. Among hospitalized mental patients the earlier diagnosis and segregation of infectious cases of tuberculosis are probably the most important causes. It must be recalled that prior to the beginning of the tuberculosis control program in the mental institutions, due to the lack of sufficient case-finding facilities, there were many persons with unrecognized tuberculosis in almost all wards of all institutions who acted as foci of infection for the rest of the ward populations. The inauguration of periodic roentgenographic examination of all patients made possible the earlier recognition and segregation of such cases, with consequent decrease of exposure of the rest of the patients.

The greater decrease in incidence among mental patients than in the general population of the State during the same time period can therefore be interpreted as evidence that improvement in environmental conditions is responsible for most of the change, since hereditary factors can hardly manifest themselves so markedly in such short periods of time.

Not only is the total incidence decreasing rapidly among mental patients, but also the rates for the individual hospitals are approaching in magnitude those estimated for the general population. For example, during the time between the first and second surveys, only one of the fifteen hospitals had rates of less than 2 new cases of tuberculosis per 1,000 person-years (two per 1,000 patients per year), while for the fourth survey period, seven had rates as low (table 5). Although the total incidence rate of 2.2 per 1,000 person-years for mental patients is still more than twice as high as that estimated for the general population of the State in the same age brackets, the rapid decrease in incidence during the past eleven years, in spite of considerable overcrowding of all mental hospitals, provides strong evidence of the effectiveness of the basic measures used to control this disease.

It may therefore be concluded that mental patients respond well to the ordinary preventive measures used in the control of tuberculosis, early diagnosis and early segregation. It may also be inferred that there is nothing inherent in mental disease per se which predisposes these patients to tuberculosis.

Tuberculosis Mortality

The higher tuberculosis death rates among mental patients as compared with the general population, shown in table 6, is one of the reasons for the impression that mentally ill patients do not react to tuberculosis as well as sane persons. Closer examination of some of the factors involved in the higher death rates, however, shows that, as in the case of morbidity from this disease, much of the

TABLE 5

INCIDENCE OF TUBERCULOSIS IN INDIVIDUAL MENTAL HOSPITALS BY SURVEY PERIODS

PERIOD BETWEEN FIRST AND SECOND SURVEYS		PERIOD BETWEEN SECOND AND THIRD SURVEYS		PERIOD BETWEEN THIRD AND FOURTH SURVEYS	
Institution	Rate per 1,000 Person-Years	Institution	Rate per 1,000 Person-Years	Institution	Rate per 1,000 Person-Years
1. Brooklyn	1.4	1. Brooklyn	1.2	1. Brooklyn	0.4
2. St. Lawrence	2.3	2. Rochester	1.7	2. Rochester	0.8
3. Manhattan	2.4	3. St. Lawrence	1.9	3. St. Lawrence	0.9
4. Willard	3.6	3. Willard	1.9	4. Manhattan	1.3
5. Gowanda	5.3	4. Manhattan	2.1	5. Gowanda	1.6
6. Hudson River	5.5	5. Buffalo	2.4	6. Creedmoor	1.8
7. Buffalo	6.3	6. Gowanda	2.8	7. Utica	1.9
7. Rochester	6.3	7. Hudson River	3.0	8. Central Islip	2.1
8. Kings Park	6.6	8. Creedmoor	3.4	9. Willard	2.5
8. Harlem Valley	6.6	9. Kings Park	3.5	9. Buffalo	2.5
9. Creedmoor	7.1	9. Marcy	3.5	10. Kings Park	2.7
10. Central Islip	7.2	10. Central Islip	3.8	11. Marcy	2.8
11. Utica	7.4	11. Harlem Valley	5.1	11. Hudson River	2.8
12. Marcy	7.7	12. Utica	5.3	12. Binghamton	3.0
13. Binghamton	8.5	13. Binghamton	6.5	13. Harlem Valley	3.7

difference in mortality between the two groups can be explained upon epidemiologic grounds other than constitutional. Among these factors are the following:

There is more tuberculosis among mental patients, so that more deaths from this disease must be expected. The high prevalence among patients on admission to the mental hospitals and the high incidence subsequently result in a much higher concentration of tuberculosis among patients within these hospitals than in the general population, so that higher death rates are inevitable.

The higher average age of mental patients as compared with the general population (fifty-three and thirty-four years, respectively) carries with it a higher tuberculosis mortality, since tuberculosis is more frequently a cause of death among older persons, especially among males, as shown in table 7. This table also shows that, when the age distribution of the State's population is adjusted to correspond with that of hospitalized mental patients, the ratio between the death rates is considerably reduced. Thus, for 1949 the rate for the State as a whole is increased about 59 per cent.

The rapid decrease in the tuberculosis death rate which has occurred among hospitalized mental patients during the past few years provides strong evidence of the importance of environmental factors upon the death rate, since changes due to constitutional factors cannot be expected to produce such results in so short a time period.

Thus, no definite trend in tuberculosis mortality among mental patients from 1935 to 1941 is shown in table 6. With the beginning of the tuberculosis control program in the fall of 1941, the rate increased considerably, probably because of the disclosure by the initial chest roentgenographic surveys of the large number of hitherto unknown cases

TABLE 6

DEATHS FROM TUBERCULOSIS (ALL FORMS) AND RATES PER 100,000 FOR PATIENTS IN MENTAL HOSPITALS AND FOR NEW YORK STATE

YEAR	MENTAL HOSPITALS		NEW YORK STATE†		RATIO OF MENTAL HOSPITALS TO NEW YORK STATE
	Number of Deaths	Rate per 100,000	Number of Deaths	Rate per 100,000	
1935	409*	676.9*	7,120	70.5	9.6
1936	418*	667.2*	7,316	71.5	9.3
1937	501*	769.7*	7,036	68.0	11.3
1938	427*	639.5*	6,276	59.9	10.7
1939	433*	633.3*	6,221	58.7	10.8
1940	461	655.5	6,071	56.6	11.6
1941	482	671.0	5,908	54.7	12.3
1942	508	688.8	5,784	53.2	12.9
1943	608	839.7	6,122	55.9	15.0
1944	561	783.8	5,845	53.0	14.8
1945	477	662.3	5,768	51.9	12.8
1946	467	635.9	5,384	48.1	13.2
1947	402	558.3	5,105	45.3	12.3
1948	410	553.1	4,971	43.8	12.6
1949	342	433.8	4,296	37.6	11.5
1950	275	353.4	3,656	31.8	11.1
1951	229	273.2	3,373	29.1	9.4

* Estimated.

† Fifteen years of age and older.

TABLE 7

TUBERCULOSIS DEATH RATES PER 100,000 (ALL FORMS) BY AGE IN MENTAL HOSPITALS AND NEW YORK STATE, 1949 AND AGE-ADJUSTED RATES FOR THE STATE BASED UPON MENTAL HOSPITAL POPULATION AGE DISTRIBUTION*

AGE	MENTAL PATIENTS	NEW YORK STATE
All ages	505.3	29.8
Less than 25	291.0	6.9
25–34	472.2	24.1
35–44	581.9	35.0
45–54	351.9	47.7
55–64	553.0	61.1
65–74	594.5	64.8
75 and older	574.0	59.1
New York State adjusted rate		47.4
Per cent increase of age adjusted rate over crude rate		59.1

* Excludes three mental hospitals located in New York City.

of tuberculosis, so that the diagnosis of tuberculosis as the cause of death was made more frequently. Since 1943 the death rate has been decreasing continuously, the rate of decrease comparing favorably with that of the State as a whole.

This decrease is particularly significant because it has occurred in spite of the much larger percentage of mental patients in the older ages. Among older persons in the general population, reductions in tuberculosis death rates have been considerably

smaller than among younger persons. Most of the decrease in mortality among mental patients is probably due to the decrease in the rate of development of the disease. This will be discussed when the prevalence of the disease is considered.

Since specific measures for the treatment of tuberculosis, such as pneumothorax and surgery, have been used only to a minimal extent and antimicrobials have not yet been used sufficiently long and upon a large enough number of patients to affect the death rate, the decrease in mortality is not yet a reflection of improvements in therapy.

The importance of coexisting organic disease must be considered with regard to its effect upon tuberculosis mortality as well as upon morbidity. If concurrent nontuberculous organic disease can lower patients' resistance to the point at which they will develop tuberculosis under conditions which ordinarily would not result in its development, it also appears reasonable to assume that this reduction in resistance may sometimes mean the difference between recovery from tuberculosis and death.

There are probably differences in the accuracy of diagnosis and reporting of tuberculosis as the cause of death which affect the relative rates in the two groups. In the general population, unless evidence of the presence of tuberculosis is definite during the life of the patient, there is a reluctance of the physician to report tuberculosis as the cause of death. The result is that some patients who do not present the characteristic symptoms and physical signs of tuberculosis during life, especially if the patients were not seen until shortly before death and were not examined roentgenographically, are incorrectly certified as having died of nontuberculous causes. Medlar (6), from his study of necropsy reports, provides some evidence in favor of this opinion, stating that: "In the older age groups the tuberculous infection frequently is not recorded either as the chief or as a contributing cause of death, even if cavity formation and pathologically active disease are present." Among hospitalized mental patients, on the other hand, since the presence of pulmonary tuberculosis is known from the routine roentgenogram, there is probably a tendency to ascribe to tuberculosis, deaths which are actually due to other causes. As a result of these opposite tendencies in certification, there is probably some understatement of tuberculosis as a cause of death in the general population and overstatement of its importance among mental patients.

Additional evidence against a constitutional inferiority as a cause of high tuberculosis death rates is presented in a recent study of the survival of tuberculous mental patients (7). This report indicates that, when such factors as age and stage of disease are taken into consideration, the survival of mental patients from tuberculosis is similar to that of sane tuberculous patients, so that the disease is not more malignant for one group than for the other.

Nor are high death rates among these patients unique for tuberculosis. The high morbidity from nontuberculous organic diseases mentioned previously is reflected in the high mortality from these concurrent diseases. It is shown in table 8 that death rates from many other individual causes, as well as the total death rate, are much higher among mental patients. Thus, if the higher mortality from tuberculosis is to be explained upon a constitutional basis, this explanation must be extended to include other diseases with higher mortality rates among these patients.

Although insufficient data are available to permit a detailed statistical consideration of the factors involved in the differences in tuberculosis mortality in the two groups, it is evident that here also, as in the case of tuberculosis morbidity, if factors of epidemiologic importance are considered, the differences between the two groups can be explained.

TABLE 8

NEW YORK STATE ACTUAL DEATH RATES, DEATH RATES ADJUSTED TO A MENTAL HOSPITAL POPULATION, MENTAL HOSPITAL DEATH RATES, AND RATIO OF MENTAL HOSPITAL DEATH RATES TO ADJUSTED NEW YORK STATE DEATH RATES 1948–1949*

CAUSE OF DEATH	NEW YORK STATE RATES†				MENTAL HOSPITAL RATES†		RATIO OF MENTAL HOSPITALS TO NEW YORK STATE ADJUSTED RATES	
	Actual		Adjusted					
	1949	1948	1949	1948	1949	1948	1949	1948
Total†	10.5	10.8	26.2	28.1	89.0	92.1	3.4	3.3
Syphilis	4.8	7.5	9.6	13.6	277.8	481.2	28.9	35.4
Malignant neoplasm	177.7	174.1	428.6	453.2	468.0	494.7	1.1	1.1
Diabetes mellitus	20.2	42.7	73.6	126.9	107.8	210.0	1.5	1.7
Intracranial lesions of vascular origin	87.2	73.5	271.3	240.9	658.3	475.4	2.4	2.0
Diseases of the heart	441.3	422.2	1,260.0	1,295.7	5,268.8	5,023.1	4.2	3.9
Diseases of arteries	25.0	23.5	88.1	90.1	370.7	430.3	4.4	4.8
Nephritis and nephrosis	12.3	40.0	28.0	119.8	33.0	166.2	1.2	1.4
Pneumonia, all forms	27.2	35.1	60.0	79.0	314.6	349.0	5.2	4.4
Accidents	52.0	57.0	105.4	128.6	120.5	327.2	1.1	2.5

* Data from Annual Reports, New York State Department of Health, Office of Vital Statistics.

† Rate of all deaths per 1,000 patients; individual causes, per 100,000.

Prevalence of Pulmonary Tuberculosis Among Patients Within Mental Hospitals

The prevalence of tuberculosis among hospitalized patients is considered last because the number of cases of tuberculosis among these patients is the result of the interaction of many factors, some of which were reviewed above, such as the morbidity upon admission and the incidence and mortality within the institutions.

At the time of completion of the initial survey in all hospitals, 4,197 cases of *clinically significant* tuberculosis were found among the patients. By the time the second survey was completed four years later, the number had decreased to 2,943, and the third survey completed four years after the second disclosed 2,102. Thus, there was a decrease of one-third in the prevalence rate between each of the surveys, while for the total period the decrease was 56 per cent (table 9).

There is no doubt that the decreasing incidence rate is one of the most important causes of this reduction in prevalence. The evidence for this opinion is based upon a weighing of the factors tending to increase the prevalence of tuberculosis against those tending to decrease it. In addition to the obvious direct effect of the reduction in incidence in reducing the number of tuberculous patients, the indirect evidence includes the following:

The decrease in total prevalence within the hospitals cannot be ascribed to any change in the prevalence on admission, since this does not show a downward trend (table 1). It may be mentioned that, although not shown in this table, there has been no significant change in the prevalence of tuberculosis on admission since the beginning of the program in 1941.

TABLE 9

PREVALENCE OF PULMONARY TUBERCULOSIS AMONG PATIENTS IN MENTAL HOSPITALS IN EACH OF THREE CHEST ROENTGENOGRAPHIC SURVEYS

	FIRST SURVEY		SECOND SURVEY		THIRD SURVEY	
	Number of Cases	Rate Per Cent	Number of Cases	Rate Per Cent	Number of Cases	Rate Per Cent
Clinically Significant*						
Total	4,197	5.7	2,943	3.8	2,102	2.5
Males	2,364	6.8	1,799	5.0	1,309	3.4
Females	1,833	4.7	1,144	2.7	793	1.7
Inactive (Apparently Cured)†						
Total	3,996	5.4	4,658	5.9	4,533	5.4
Males	1,994	5.7	2,306	6.4	2,181	5.6
Females	2,002	5.2	2,352	5.6	2,352	5.1
Total Tuberculosis						
Total	8,193	11.1	7,601	9.7	6,635	7.8
Males	4,358	12.5	4,105	11.4	3,490	9.0
Females	3,835	9.9	3,496	8.3	3,145	6.8

* Clinically significant: Cases of pulmonary tuberculosis classified as *active*, *quiescent*, *apparently arrested*, or *arrested* in the 1940 edition of *Diagnostic Standards*, published by the National Tuberculosis Association, or as *active* or *arrested* in the 1950 edition.

† Cases classified as *apparently cured* in the 1940 edition of *Diagnostic Standards* or as *inactive* in the 1950 edition are considered not clinically significant.

The rate of discharge of tuberculous patients from the hospitals has probably not changed materially during the time period covered by this report.

As specific measures for the treatment of tuberculosis, such as pneumothorax and surgery, have been used only to a minimal extent, and chemotherapy has not yet been used sufficiently long and upon a large enough number of patients to materially affect the number reaching a state of apparent cure of their disease, specific therapy is not considered as an important cause of the decrease in prevalence.

An increase in the number of patients whose disease reaches a state of inactivity (*apparently cured* in 1940 NTA *Diagnostic Standards*) would decrease the number of patients with clinically significant disease. In this case, however, the *total* amount of tuberculosis, the clinically significant plus that of no clinical significance, would remain unchanged. As shown in table 9, however, the total amount of tuberculosis has decreased, chiefly because of the reduction in the number of clinically significant cases, so that the rate of inactivation of the disease is not a factor.

Since the admission, discharge, and recovery rates remain essentially unchanged during this period, the decrease in tuberculosis death rates since 1943, shown in table 6, should tend to increase the prevalence of clinically significant tuberculosis. Therefore, the reduction in prevalence is not due to changes in death rates.

As none of these factors is of significance in affecting the prevalence rate, it is concluded that the reduction in incidence is the main cause of the lower prevalence.

The evidence pointing toward the decrease in incidence as of major impor-

tance in the reduction in the number of cases of tuberculosis is considered in some detail because the incidence rate is susceptible to change by changing environmental conditions within the hospitals. The early segregation of tuberculous patients produces the same results by reducing exposure as are obtained in other infectious diseases, i.e., reduction in the rate of development of new cases. The decreasing tuberculosis prevalence rate among these patients is therefore explainable in the same epidemiologic terms as in other infectious diseases, namely, reduction of exposure.

Because of the impression among psychiatrists that schizophrenic patients differ in their reaction to tuberculosis from patients with other types of mental disease (8), this subject needs mention in this report, though it will be considered in more detail in a later communication.

Preliminary review of the available data indicates that the prevalence of tuberculosis among schizophrenic patients at the time of admission, and the incidence, mortality, and prevalence rates during their residence in mental hospitals, are in general quite similar to those of patients with other mental diseases. Where differences in tuberculosis morbidity and mortality exist between schizophrenic patients and other patients, or between schizophrenic patients and the general population of the State, they can be explained largely upon the same epidemiologic grounds used in this paper for mental patients as a group.

Discussion of the effect of sex and race are also omitted because these factors have been found not to affect materially the results of this study.

SUMMARY

Tuberculosis morbidity and mortality rates are much higher among mental patients than in the general population. This is considered by some to be due to a constitutional susceptibility of mental patients to tuberculosis, implying that the methods ordinarily applicable in the control of tuberculosis may have to be intensified to an impracticable degree.

An attempt has been made to explain the higher rates upon an epidemiologic basis, and it is contended that the control measures used for the population as a whole are effective for mental patients.

The higher prevalence of tuberculosis among patients at the time of admission to mental hospitals is mainly due to differences in age distribution, to the population groups or areas from which they come, and to the presence of other coexisting organic disease.

The higher incidence of tuberculosis among mental patients is primarily due to greater exposure and opportunity for infection.

The higher tuberculosis death rates among mental patients are due to the greater prevalence and incidence of the disease, to the higher average age of mental patients, to the presence of coexisting disease, and to differences in accuracy of certification of tuberculosis as a cause of death.

The high prevalence of tuberculosis among hospitalized mental patients is due to the high rate upon admission and to the high incidence rate within the institutions.

Thus, the higher prevalence, incidence, and mortality rates can be explained by differences in factors of epidemiologic importance between mental patients and the general population.

The rapid decrease in morbidity and mortality during the past twelve years indicates that the changes are due to improvement in environmental factors, chiefly early diagnosis and segregation.

It is concluded that, since the high morbidity and mortality among mental patients can be explained upon an epidemiologic basis, within the concept of tuberculosis as an infectious disease, there is no need to consider that these high rates result from a greater degree of constitutional lack of resistance which renders these patients more susceptible to tuberculosis than normal persons.

SUMARIO

La Morbidad y la Mortalidad Tuberculosas entre los Psicópatas Comparados con la Población General

Los coeficientes de morbilidad y mortalidad tuberculosas son mucho más altos entre los psicópatas que entre la población general. Consideran algunos que eso se debe a una susceptibilidad constitucional de esos enfermos a la tuberculosis, dando a entender que tal vez haya que intensificar en forma impracticable los métodos aplicables ordinariamente a la lucha antituberculosa.

Trátase aquí de explicar a base epidemiológica esos coeficientes más altos, arguyéndose que las medidas de lucha usadas para la población en conjunto son también eficaces para los enfermos psiquiátricos.

La mayor frecuencia de la tuberculosis entre los enfermos a su ingreso en los frenocomios se debe principalmente a diferencias en la distribución por edades, los grupos o zonas de población de donde vienen y a la presencia de otra coexistente afección orgánica.

La incidencia más alta de la tuberculosis entre los psicópatas se debe primordialmente a mayores exposición y ocasiones de infección.

Los coeficientes más altos de mortalidad tuberculosa entre los psicópatas se deben a la mayor frecuencia e incidencia de la enfermedad y a diferencias en la exactitud de la mención de tuberculosis como causa de muerte.

La elevada frecuencia de la tuberculosis entre los psicópatas hospitalizados procede de la tasa elevada de la enfermedad al ingreso y a la elevada incidencia en las instituciones.

Por lo tanto, cabe explicar los coeficientes más altos de frecuencia, incidencia y mortalidad por las diferencias en factores de importancia epidemiológica entre los psicópatas y la población general.

La rápida disminución de la morbidad y la mortalidad durante los últimos doce años indica que los cambios se deben a mejoras en factores del medio ambiente, y principalmente al diagnóstico y a la segregación tempranos.

Visto que cabe explicar las elevadas morbidad y mortalidad tuberculosas entre los psicópatas a base epidemiológica, dentro del concepto de la tuberculosis como enfermedad infecciosa, no hay necesidad de considerar esos coeficientes altos como debidos a una falta mayor de resistencia orgánica que susceptibiliza a esos enfermos más que a las personas normales a la tuberculosis.

RESUME

Morbidité et mortalité par tuberculose parmi les malades mentaux par rapport à la population générale

Les taux de morbidité et de mortalité par tuberculose sont beaucoup plus élevés parmi les malades mentaux que dans la population générale. Certains considèrent que ceci est dû à

l'existence d'une susceptibilité constitutionnelle du malade mental pour la tuberculose, ce qui impliquerait la nécessité d'intensifier à un degré impraticable les méthodes ordinairement applicables à la lutte contre la tuberculose.

Les auteurs tentent d'expliquer ces taux élevés sur une base épidémiologique, ils estiment que les mesures utilisées contre la tuberculose pour l'ensemble de la population s'appliquent efficacement aux malades mentaux.

La prédominance élevée de la tuberculose rencontrée parmi les malades mentaux au moment de l'admission dans les hôpitaux psychiatriques, est surtout due aux différences de distribution dans les groupes d'âge, groupes de population ou régions dont ils sont issus et à la présence d'une d'autre affection organique coexistante.

L'incidence plus élevée de la tuberculose parmi les malades mentaux est principalement imputable aux conditions plus favorables à la contamination.

Les taux de mortalité par tuberculose plus élevés enregistrés parmi les malades mentaux hospitalisés sont dûs à une prédominance et à une incidence plus élevées de l'affection et, aussi, aux différences dans l'exactitude des certificats de décès en ce qui concerne la tuberculose.

La prédominance élevée de la tuberculose parmi les malades mentaux est imputable au taux élevé de la tuberculose à l'admission et au taux d'incidence élevé à l'intérieur de l'établissement.

Ainsi la prédominance, l'incidence et les taux de mortalité plus élevés s'expliquent par l'existence de différences dans les facteurs épidémiologiques entre les malades mentaux et la population générale.

La décroissance rapide de la mortalité et de la morbidité dans ces douze dernières années indique que ces changements sont dûs à l'améliorations des facteurs concernant le milieu, surtout le diagnostic et les mesures d'isolement.

Etant donné que la morbidité et la mortalité élevées chez les malades mentaux peuvent s'expliquer selon une base épidémiologique, et considérant la tuberculose comme une maladie infectieuse, il n'y a pas lieu d'attribuer ces taux élevés à un plus haut degré de manque de résistance constitutionnelle, qui rendrait ces malades plus sensibles à la tuberculose que les individus normaux.

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TUBERCULOSIS AND ABORTION[1]

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INTRODUCTION

Whether therapeutic abortion is indicated in the patient with tuberculosis has been the subject of a great many articles. The difficulty in evaluating the end results of the various forms of treatment or procedures to which the patient with tuberculosis is subjected is well known. The chronicity of the disease, the tendency to recurrence after apparent arrest, the patient's resistance, allergy, age, and nutrition are but a few of the factors which vary from one person to another. Even greater difficulty is encountered when the efficacy of different procedures is compared in the tuberculous patient, for it is obvious that no two patients can be found of similar age, onset, type, and extent of disease who received exactly the same treatment. Furthermore, the reaction to either pregnancy, delivery, or abortion varies greatly, not only from patient to patient, but also in the same person at different times, so that precise statistical deductions are not possible. The recent medical and surgical advances in the treatment of tuberculosis have greatly altered our concepts concerning the prognosis. The present report is concerned with the results following therapeutic and spontaneous abortion in the tuberculous patient with the consideration of the present management of this complication of pregnancy.

MATERIAL

The present report is based on 100 consecutive abortions in tuberculous patients treated at the New York Lying-In Hospital from September, 1932, to January, 1952. The type of patients treated is presented in figure 1.

OBSERVATIONS

Incidence

In the period of almost twenty years under consideration, there were 67,232 obstetrical discharges from the hospital (61,732 full-term and premature deliveries and 5,500 abortions). Of this number, 665 (0.98 per cent) had tuberculosis complicating pregnancy; 565 had full-term or premature deliveries; 66 (0.098 per cent) had therapeutic abortions; and 34 had spontaneous abortions.

For the entire period, 10.4 per cent of all patients admitted with tuberculosis had therapeutic abortions performed. From 1932 to 1937, this figure was 23 per cent, whereas from 1948 through 1951, it had dropped to 3.7 per cent. This decrease in the last five-year period, which amounts to one-sixth that of the rate in the first five-year period, is even more extensive in present practice. Indeed,

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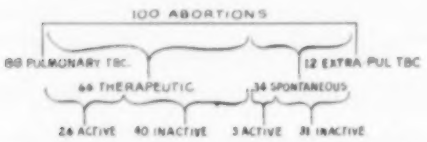

FIG. 1. Summary of abortions in tuberculous patients at New York Lying-In Hospital (1932–1952).

there have been no therapeutic abortions for tuberculosis on the ward service during the past three years.

The policy, in effect since 1945 at The New York Lying-In Hospital, of obtaining a routine photoroentgen of the chest in all clinic antepartum patients has resulted in a threefold increase in the recognized incidence of pulmonary tuberculosis. In the past few years, the incidence has approached 2 per cent of those examined. Such an examination should be obtained when the patient is first seen, and the present experience suggests that it could be profitably repeated during the last trimester of pregnancy (1).

Therapeutic Abortion

Indications: At the present time, tuberculosis is rarely an indication for therapeutic abortion at the Lying-In Hospital. A decade or more ago, however, approximately 20 per cent of the patients admitted to the hospital with tuberculosis were aborted. During the entire period, 28 per cent of the patients with active disease and 9 per cent of those with inactive disease were aborted. An attempt to determine from the charts the reason for aborting some patients and not others with inactive disease has not been successful. Frequently, the only indication that appeared was "tuberculosis"; yet financial, sociologic, or psychologic reasons may have existed which prompted the doctor to decide on abortion. It should be recalled that up to a few years ago, before antimicrobial therapy and excisional surgery became available, the prognosis for tuberculosis presented many uncertain aspects. It was, and still is, hazardous to predict which lesion will break down and which will not, especially in the postpartum period when the mother's energies are directed toward her infant and household and away from her own health.

Mental as well as physical rest is important for proper healing of the tuberculous process, and a breakdown caused by the patient's fear of pregnancy, whether fancied or real, may have influenced the physician to recommend therapeutic abortion. Perhaps a few patients did not desire to continue with their pregnancy and tuberculosis presented a legal indication for termination. Some phthisiologists did not wish any "extraneous" circumstances to interfere with the cure of their patient and recommended abortion more frequently than others.

Follow-up observations: To evaluate the effect of therapeutic abortion (or full-term delivery) on the tuberculous patient, a sufficient period of follow-up should be available. Improvement or progression of the disease within three months of

abortion or delivery may properly be attributed to the pregnancy or to the procedure of termination, although such changes may have occurred before or during the pregnancy and may continue their course after it. On the basis of experience with inpatients in tuberculosis hospitals who could be carefully followed for long periods of time, the writers have chosen a minimum period of three months for follow-up, except for patients in whom changes became manifest before that time (2).

It is noteworthy that 32 per cent of the patients who had therapeutic abortions were lost to follow-up observation within one week of termination of their pregnancy, and an additional 12 per cent were lost within three months. In contrast to these patients on whom therapeutic abortion was performed and who were not followed for more than three months (44 per cent of the aborted group), only 16 per cent of the patients who had full-term or premature deliveries were lost from observation within the first three months post partum. Equal efforts were made to keep both groups of patients under observation. This is in support of the impression of the present writers that some of the patients used "tuberculosis" as an excuse to be aborted and did not permit further treatment of their tuberculosis. One of the present writers (G. S.), as a consultant to a tuberculosis hospital, has frequently seen abortions performed on patients who then signed themselves out against advice after several days, only to return within a year with far advanced, progressive tuberculosis.

The results in patients who were aborted because of the presence of tuberculosis during the period from September, 1932, to January, 1952, at the Lying-In Hospital are presented in table 1. Although only 37 patients were followed longer than three months after abortion, 2 patients became worse within three months and are included in the results.

Patients with active tuberculous lesions: Because of the terminology used in the earlier years, it was necessary to classify the disease of the patients as *active* or *inactive* rather than follow the preferable National Tuberculosis Association classification of minimal, moderately advanced, or far advanced. Of the 15 patients with *active* tuberculosis, 2 improved. In one, a thoracoplasty was performed three years after abortion; and, in the second, improvement occurred after two years of sanatorium treatment. One patient with *active* far advanced bilateral disease who died ten days after operation had been seriously ill at the time the operation was performed.

TABLE 1

RESULTS IN THERAPEUTIC ABORTION AFTER THREE MONTHS' FOLLOW-UP

TYPE OF DISEASE	NUMBER	IMPROVED	UNCHANGED	PROGRESSED	DIED
Active	15	2	7	5*	1
Inactive	24	0	21	1	2
Total	39	2	28	6	3

* Two patients became worse within three months of abortion.

In 7 patients, the tuberculosis was unchanged following abortion, whereas in 5 the disease progressed. In 2 patients, progression of the disease continued following abortion and was apparent while the patient was still in the hospital. One of these patients (1951) had moderately advanced pulmonary tuberculosis and continued to run a febrile course following dilatation and curettage. The second (1947) had moderately advanced pulmonary tuberculosis with cavity formation. An abdominal hysterotomy was done, following which this patient received streptomycin. However, she left the hospital against advice two weeks postoperatively, at which time her tuberculosis was steadily progressing.

The third patient (1936) whose tuberculosis progressed had moderately advanced disease with cavity formation and continued to show a spread of her disease following dilatation and curettage. Nine months following abortion, her disease was still uncontrolled.

The fourth patient (1937) had far advanced tuberculosis with a cavity. She received pneumothorax following a dilatation and curettage at two and one-half months' gestation but continued to show a progression of her disease at follow-up examination three years later.

The fifth patient (1941) had pulmonary tuberculosis of questionable activity on admission. A dilatation and curettage was done at two and one-half months' gestation, and follow-up examination six years later showed the patient to have bilateral far advanced disease.

Comment: No definite conclusions are warranted from this small group of patients. The improvement which occurred in the 2 patients with active disease was noted so long after the abortion (two and three years, respectively) that it was probably unrelated to the procedure. Likewise, the patient who died had such far advanced disease that the abortion presumably did not influence the outcome. In 7 patients, the tuberculosis remained unchanged for the follow-up period. In these patients, the abortion neither improved nor worsened their tuberculosis. The 5 patients who became worse following abortion showed a continued progression of their disease while in the hospital and after discharge. Whether this progression would have occurred if abortion were not done cannot be determined.

Inactive patients: Twenty-four patients with inactive tuberculosis were aborted. In 21, the disease remained unchanged, in one it progressed, and 2 died following operation. The 2 deaths in the patients with inactive disease were not related to the abortion. One patient died of carcinoma of the breast two months after abortion; and the second, of tuberculous meningitis four years after abortion. The patient with inactive disease which reactivated following abortion had had apparently arrested disease for six years before a dilatation and curettage was done. One year following operation her tuberculosis reactivated. It is questionable whether the abortion had anything to do with the exacerbation of the tuberculosis. The great majority of the patients with inactive disease, 21 of 24, showed no change in their tuberculosis for long periods after abortion. It appeared that, in patients with inactive tuberculosis, the performance of a therapeutic abortion did not affect their condition.

Type of procedure: In 3 instances, the cervix was dilated and a packing inserted under morphine and scopolamine analgesia, and the products of conception were extruded or removed with a sponge stick several days later. Fifty-seven patients had a dilatation and curettage performed under either general or local anesthesia. Of the 6 patients who had abdominal hysterotomy, 3 had extrapulmonary disease and only one of the 6 had active pulmonary disease. In the one patient with active pulmonary tuberculosis, the disease progressed within three months of the gynecologic procedure.

One patient with arrested pulmonary disease, who had had a radical operation for carcinoma of the breast one year before abortion, died of generalized carcinomatosis two months after abdominal hysterotomy. The third patient with inactive pulmonary disease had an abdominal hysterotomy and tubal ligation and showed no change in her condition.

Extrapulmonary tuberculosis: The 3 patients with extrapulmonary disease were all in an inactive stage when abdominal hysterotomy was performed and are mentioned briefly because of their interesting histories. The first patient had a pericardectomy for a tuberculoma in 1936. An abdominal hysterotomy and tubal ligation was done in 1937 and follow-up for fifteen years revealed that the patient is in good condition. The second patient had a nephrectomy for tuberculosis in 1939. Following abdominal hysterotomy and tubal ligation in 1942, she has shown no change in her condition. The third patient had kyphoscoliotic heart disease as well as arrested Pott's disease of the spine. The indication for the hysterotomy was probably the heart disease. No tubal ligation was performed, and the patient returned twice in the following twelve months for therapeutic abortions. Dilatation and curettage was done on each occasion.

Although the number of patients who had abdominal hysterotomy is small, once again the patients with inactive disease showed no change in their condition following the procedure, whereas the one patient with active disease continued to progress. One of the present writers (G. S.) reported on 63 patients who had therapeutic abortion at tuberculosis hospitals, twenty of which were performed by vaginal or abdominal hysterotomy. Eight of the 20 patients (40 per cent) died, whereas only 4 of 43 patients (9 per cent) died in whom dilatation and curettage was done (3).

Comment: The present writers believe, along with others, that interruption of pregnancy by abdominal or vaginal hysterotomy after the first trimester in the patient with active tuberculosis is not indicated. Continuation of the pregnancy plus antimicrobial drugs and excisional surgery, when indicated, offer the patient a better chance of recovery. In a number of patients with active pulmonary tuberculosis, the disease has been controlled by the use of antimicrobial drugs during pregnancy, and improvement has continued after delivery. Furthermore, 2 patients have been delivered who have had lobectomies for tuberculosis performed during gestation. Both patients have improved, and one has been delivered a second time (4).

There may be several reasons why improvement does not follow abdominal or vaginal hysterotomy performed in the patient with active disease even though

she too receives antimicrobial therapy. First, she cannot be kept under as strict surveillance for an additional five or six months (the remainder of the antepartum and postpartum care) as is the patient who continues her pregnancy. Not infrequently, the former either interrupts or discontinues her antimicrobial therapy with dire results. Second, it has been postulated from animal experimentation that estrogen exerts a favorable effect on resistance to tuberculosis. Presumably, this effect is produced by retarding the progress of the disease by reducing the permeability of the connective tissue and its capillaries. Moreover, it has been shown that estradiol dipropionate uniformly retards the tuberculous process at the site of inoculation in the skin of inbred rabbits (5–7). To what extent these data apply to human tuberculosis is problematical, since the amount of estrogen used in the animals far exceeded the physiologic levels in humans. However, the sudden decrease in estrogenic hormone resulting from interruption of pregnancy at a time when the hormone has reached high levels (in the second trimester of pregnancy) may be another factor involved in the poorer results following abortion.

A third factor, and one difficult to evaluate, is the psychologic effect produced on the patient following abdominal hysterotomy when the fetus is formed. Such patients frequently inquire about the sex, size, organ formation, et cetera, and exhibit a feeling of guilt which may persist for a long period of time and is not conducive to proper mental rest. Some patients become greatly depressed because they consider their condition is hopeless and think that for this reason they are not being permitted to continue with the pregnancy. This is in marked contrast to the patient with active disease who continues with the pregnancy, gains weight, and often expresses the opinion that she is not wasting time being confined to the hospital for treatment of her tuberculosis since she will leave with a baby.

Spontaneous Abortion

Thirty-four spontaneous abortions occurred in patients with tuberculosis, an incidence of 5 per cent of all pregnant patients with tuberculosis admitted to the hospital. As the incidence of spontaneous abortion in nontuberculous patients at the Lying-In Hospital during this period was 9 per cent, the notion that tuberculosis is a frequent cause of spontaneous abortion was not supported. Thirty spontaneous abortions occurred in patients with pulmonary tuberculosis, of whom only 2 had active disease. One of these patients died of diffuse miliary tuberculosis four days post partum after aborting at twenty weeks' gestation, and the second showed no change in her condition three years later. The remaining 26 patients with inactive pulmonary tuberculosis (who had 28 spontaneous abortions) were all unchanged with respect to the disease. (Follow-up for longer than three months was possible in 68 per cent of these patients.)

Four patients with nonpulmonary tuberculosis aborted; 3 with inactive tuberculosis and one with active tuberculous peritonitis and endometritis. The latter patient had a spontaneous abortion at eleven weeks' gestation in 1946. Fourteen days following discharge from the hospital she had profuse vaginal bleeding and

severe lower abdominal pain, for which she was readmitted to the hospital. A dilatation and curettage revealed necrotic decidua and tuberculous endometritis. Eight days later an exploratory laparotomy was done, and generalized tuberculous peritonitis and tuberculosis of the omentum (biopsy) was found. A recent follow-up observation on the patient reveals she is still alive, but no pelvic examination is recorded.

Completion of the spontaneous abortion by curettage was done in 27 of 34 instances. With the exception of the patient who aborted at twenty weeks, all other abortions occurred within the first trimester.

In summary: Of 34 spontaneous abortions which occurred in 32 patients with tuberculosis, 3 were in patients with active disease, which was fatal in one patient and remained unchanged in the other 2. Twenty-nine of the abortions occurred in patients with inactive disease which, in every instance, remained unchanged following abortion. In the patients with inactive tuberculosis, spontaneous abortion apparently had no effect on the course of the tuberculosis, either pulmonary or extrapulmonary.

Comparison of Abortions with Full-Term and Premature Deliveries

Comparison of different procedures in tuberculous patients leaves much to be desired. Although the figures for the therapeutic abortion group are presented together with those for full-term and premature deliveries, the percentages alone do not give the entire answer to the problem. While follow-up observations for periods longer than three months were possible in only 56 per cent of the 66 patients who had therapeutic abortions, 84 per cent of the 565 patients who had full-term and premature deliveries were followed from three months to nineteen years. The significance of the period of longer observation, which enabled longer and more adequate treatment, on the better end results in the latter group has been mentioned above.

The results following full-term and premature deliveries after follow-up longer than three months are shown in table 2.

Active tuberculosis: The 2 patients who died did not have the advantage of prenatal care, and both had far advanced active pulmonary tuberculosis. The first patient was admitted from another state shortly before delivery, and the second was an unregistered patient admitted in active labor who died five hours after delivery. Post-mortem examination revealed extensive tuberculous pneumonia.

TABLE 2

RESULTS IN FULL-TERM AND PREMATURE DELIVERY AFTER FOLLOW-UP OF THREE MONTHS OR LONGER

TYPE OF DISEASE	NUMBER	IMPROVED	UNCHANGED	PROGRESSED	DIED
Active	66	37	25	2	2
Inactive	395	6	380	9	0
Total	461	43	405	11	2

TABLE 3

RESULTS IN ACTIVE TUBERCULOSIS FOLLOWING THERAPEUTIC ABORTION COMPARED WITH FULL-TERM AND PREMATURE DELIVERY

RESULT	THERAPEUTIC ABORTION (15)	FULL-TERM AND PREMATURE DELIVERY (66)
	per cent	*per cent*
Improved	13	56
Unchanged	47	38
Progressed	33	3
Died	7	3
	100	100

TABLE 4

RESULTS IN INACTIVE TUBERCULOSIS FOLLOWING THERAPEUTIC ABORTION AND DELIVERY

	THERAPEUTIC ABORTION (24)	DELIVERY (395)
	per cent	*per cent*
Improved	0	1.5
Unchanged	88	96.0
Progressed	4	2.5
Died	8	0.0
	100	100.0

Only 2 patients with active tuberculosis showed a progression of their disease; in 37 the disease improved; and in 25 it remained unchanged. In table 3 is presented a comparison of results (expressed in per cent) following therapeutic abortion and full-term and premature delivery in patients with active tuberculosis.

Thirteen per cent of the patients on whom therapeutic abortion was performed experienced improvement of their tuberculosis after operation, compared to 56 per cent who improved after full-term or premature delivery. Of significance is the fact that 33 per cent of the patients who were aborted had subsequent progression of disease, compared to only 3 per cent who experienced progression following delivery.

Another factor, and one which prevailed before the era of chemotherapy, which may have been responsible for the better results following full-term delivery was that, when abortion was contemplated, active treatment for the tuberculosis was frequently delayed until six or eight weeks after termination of the pregnancy. In a patient whose disease was active and progressing, such a delay might have meant the difference between a successful or unsuccessful result.

Inactive tuberculosis: The results in per cent following therapeutic abortion and full-term and premature delivery in patients with inactive tuberculosis are shown in table 4.

TABLE 5

RESULTS IN INACTIVE TUBERCULOSIS FOLLOWING ABORTION AND DELIVERY

RESULTS	THERAPEUTIC ABORTION (24) PLUS SPONTANEOUS ABORTION (19)	DELIVERY (395)
	per cent	*per cent*
Improved	0.0	1.5
Unchanged	93.0	96.0
Progressed	2.3	2.5
Died	4.7	0.0
	100.0	100.0

Comparison of the results in the patients with inactive disease reveals no significant difference. The 2 patients (8 per cent) who died following therapeutic abortion were cited above as deaths not due to the abortion. (One died of carcinoma of the breast, and one died of tuberculous meningitis four years later.) In the great majority of patients with inactive disease (88 per cent who had abortions, and 96 per cent who had deliveries), the tuberculosis remained unchanged. Progression of the disease occurred following 4 per cent of the abortions and 2.5 per cent of the deliveries.

Results Following Spontaneous and Therapeutic Abortion

Active disease: No marked difference is apparent if there are added to the 15 patients with active tuberculosis who had therapeutic abortions (table 1) and were followed longer than three months the 3 patients with active tuberculosis who had spontaneous abortions with adequate follow-up. (Two patients who had spontaneous abortions were unchanged, and one died.) The number of patients whose disease improved decreases from 13 to 11 per cent; of those with unchanged disease rises from 47 to 50 per cent; of those showing a progression of their disease decreases from 33 per cent to 28 per cent; and of those who died rises from 7 per cent to 11 per cent. Thus, the total per cent of the patients whose disease progressed to death is almost identical for both groups.

Inactive disease: Addition of 19 patients with inactive tuberculosis who aborted spontaneously and were followed longer than three months to the 24 patients (table 4) with inactive disease who had therapeutic abortions brings the results closer to those following full-term delivery. By the same token, these results are not much at variance with those of therapeutic abortion. These data are shown in table 5.

DISCUSSION

The results following 66 therapeutic and 34 spontaneous abortions in patients with tuberculosis treated at the New York Lying-In Hospital from September, 1932, to January, 1952, have been presented. Until 1947, approximately 20 per cent of the patients with tuberculosis admitted to the hospital had therapeutic abortions. From 1948 through 1951, this figure decreased to 3.7 per cent and is

even lower at the present time. While the marked dimunition in the number of therapeutic abortions performed for tuberculosis coincided with the advent of antimicrobials and excisional surgery for this disease, other factors undoubtedly played an important role.

From clinical observation it became apparent that the act of aborting a patient did not necessarily improve the end result of the tuberculous disease. Statistical analysis of this series bears out this fact although, as was mentioned above, it is realized that statistics alone may be unreliable. There was no marked difference in the results among the patients with inactive disease who were followed for periods of three months or longer and who had therapeutic abortions, spontaneous abortions, or full-term or premature deliveries. This group of patients with inactive lesions comprised 85 per cent of the total. As no deleterious effect resulted from permitting these patients to continue their pregnancy, there appears to be no valid reason on medical indications alone for aborting a patient with inactive tuberculosis.

Although the number of patients with active tuberculosis is admittedly small, 15 had therapeutic abortions, 3 had spontaneous abortions, and 66 had full-term or premature deliveries. The results, as shown in table 3, reveal a higher per cent of patients who died or suffered progression of their disease after therapeutic abortion than after full-term and premature delivery. One of the writers (G. S.) has reported a series of patients from a tuberculosis hospital, all of whom had far advanced active pulmonary tuberculosis and were admitted to the hospital in the first trimester of pregnancy (1). Forty-one had therapeutic abortions, and 43 went on to full-term delivery. Of the 41 patients who had therapeutic abortions, 10 per cent died within three months of operation, 20 per cent experienced progression and died four months or longer after abortion, 53 per cent had an unchanged course, and 17 per cent were improved. Of the 43 patients who had full-term deliveries, 7 per cent died within three months, 7 per cent experienced progression and died four months or more after delivery, 37 per cent had an unchanged course, and 49 per cent were improved.

Although in the present study, equal efforts were made to keep both groups of patients under observation, only 56 per cent of the patients who had therapeutic abortion could be followed for three months or longer, whereas 84 per cent of the full-term and premature group were followed for this period of time. While it may be argued that, if the patients who were aborted permitted themselves to be treated for longer periods, their results might have been better, the fact remains that a large number do not persist in adequate treatment for their tuberculosis. Many express the opinion that the abortion is sufficient treatment and sign themselves out of the hospital. Another factor which may have had a bearing on the better results following full-term and premature delivery was that there was no delay in instituting treatment in these patients. When abortion was contemplated, however, active treatment for the tuberculosis was delayed until after termination of the pregnancy, sometimes for six to eight weeks. (Most of these patients were treated before 1947, when antimicrobial therapy became available.)

It is the present policy in this clinic to admit all patients with active tuberculosis to the hospital and to treat them as indicated for their tuberculosis. A considerable number of patients have now received streptomycin, para-aminosalicylic acid (PAS), and isoniazid in various combinations during all stages of their gestation, with good results in the control of the tuberculous lesions and with no apparent untoward effects on their offspring. This arrest in the progression of the tuberculous lesions by the antituberculous drugs will be further reason to permit the pregnancy to continue to term, so that the condition "progressive pulmonary tuberculosis" will seldom be tenable as an indication for therapeutic abortion.

Nevertheless, each patient's case must be individualized. Recently, at another hospital, one of the writers observed a 22-year-old single girl, two months pregnant, who had severe, bilateral, far advanced pulmonary tuberculosis. She had been receiving antimicrobial therapy for three years without control of her disease, and her physician's prognosis for her was extremely poor. This was her fourth pregnancy in the past four years, during which time she had had one living child, one therapeutic abortion, and one spontaneous abortion. Therapeutic abortion was advised and performed in this patient.

SUMMARY

The incidence of therapeutic abortion for pulmonary tuberculosis at The New York Lying-In Hospital has shown a marked decrease since 1947 so that, at the present time, tuberculosis is rarely an indication for abortion. Both the clinical experience and statistical review indicate that abortion does not improve the end results in tuberculous patients. Indeed, in some instances it would appear that the results are not as good following this procedure as they are after full-term delivery.

SUMARIO

La Tuberculosis y el Aborto

La incidencia del aborto terapéutico por tuberculosis pulmonar en el hospital de Maternidad de Nueva York ha revelado una notable disminución desde 1947, de modo que, actualmente, dicha enfermedad constituye raramente una indicación de aborto. Tanto las observaciones clínicas como el estudio estadístico indican que el aborto no mejora los resultados terminales en las tuberculosas, y en realidad, en algunos casos parece que los resultados no son tan buenos con dicho procedimiento como lo son tras un parto a término. Discútense los various factores que intervienen en esto.

RESUME

Tuberculose et avortement

L'incidence de l'avortement thérapeutique pour tuberculose pulmonaire au "New York Lying-In Hospital" a subi une réduction marquée depuis 1947; à présent la tuberculose est rarement une indication de l'avortement. Les résultats cliniques de même que les analyses statistiques indiquent que l'avortement n'améliore pas les résultats éloignés de la tuberculose chez la femme tuberculeuse; en fait, dans quelques cas, il semble que les résultats observés à la suite de cette intervention ne sont pas aussi bons qu'après un accouchement à terme. Les divers facteurs en cause sont analysés.

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SUTURE LIGATION OF THE LUNG AND PARTIAL THORACOPLASTY IN THE TREATMENT OF TUBERCULOSIS[1]

A Four-Year Experience

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INTRODUCTION

In a previous report, the writers described the initial experiences with a technique of partial thoracoplasty and suture ligation of the upper portion of the lung in the treatment of pulmonary tuberculosis (1). This experience indicated that the procedure represented was a safe, nondeforming, single-stage operation which effectively controlled disease in a high percentage of selected cases of moderately advanced and far advanced tuberculosis of the upper lung. Loss of respiratory function was minimal, and the technique was successfully applied to bilateral lesions.

The present study has been made, after a four-year experience, to determine the later course of early successful cases, to ascertain more clearly the indications and contraindications of the procedure, and to evaluate its place in the general program of surgical therapy for pulmonary tuberculosis.

TECHNIQUE

The procedure was devised and first applied by Dr. Fernando Paulino of Rio de Janeiro (2, 3). The partial thoracoplasty and extensive apicolysis are performed with the patient in the lateral decubitus, through a parascapular incision, according to the technique of Carl Semb (4), and consists in the removal of the second rib, the posterior two-thirds of the third rib, and the posterior half of the fourth rib. The ribs are divided posteriorly at the lateral extremity of the vertebral transverse processes (figure 1). Beginning at or near the apex, the lung with the overlying pleura, fascia, and intercostal structures is freed from the thoracic wall and mediastinum to well below all palpable pulmonary lesions. The pneumonolysis is limited below by the hilum of the lung, although the lysis may be carried lower posteriorly if necessary.

The unique feature of the Paulino procedure consists in grasping the apex of the lung firmly with a large curved clamp and placing, from above downward, three or more concentric sutures of No. 10 crochet cotton about the lung and the overlying structures. These are drawn up to collapse snugly, compress gently, and fix the diseased lung tissue. The diseased lung is constricted within the ligatures and is not inverted downward by them (figure 2).

Material

The operation was performed forty-two times in 38 cases, as a unilateral operation in 34 and as a bilateral procedure in 4. The series included 33 whites and 5 nonwhites; 27 males and 11 females. Three-fourths of the group were patients in the Charity Hospital in New

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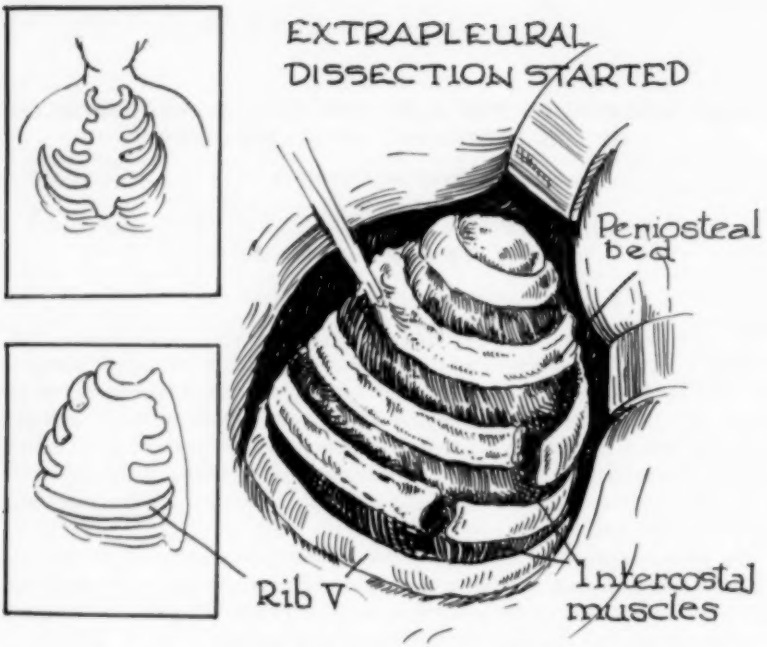

FIG. 1. Technique of Paulino procedure. Extent of rib resection.

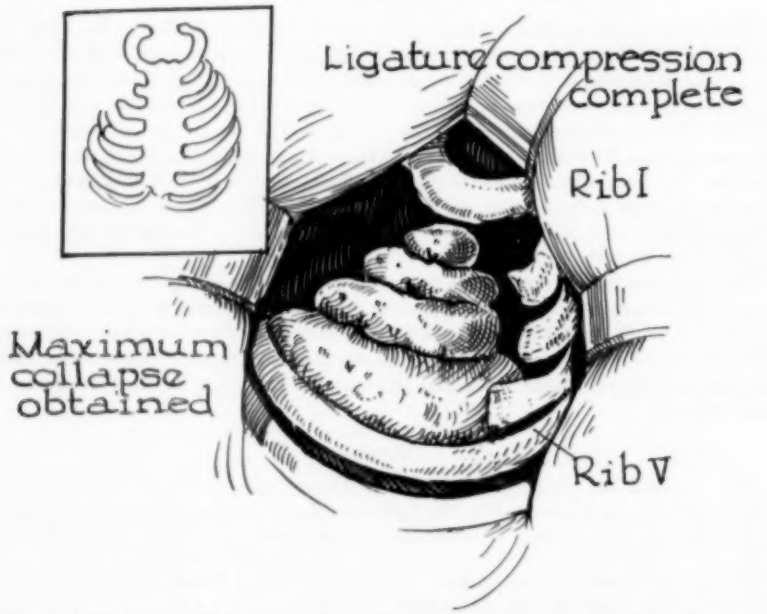

FIG. 2. Technique of Paulino procedure. Extensive pneumonolysis and suture ligation of the upper lung.

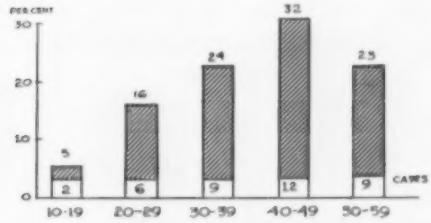

FIG. 3. Age incidence of 38 patients subjected to the Paulino procedure.

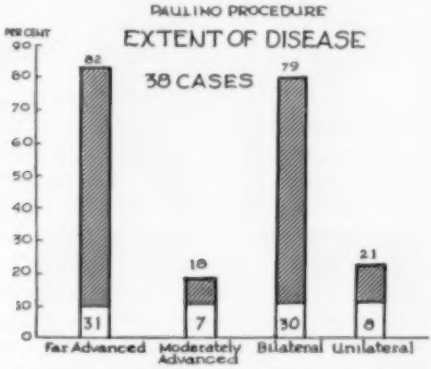

FIG. 4. Extent of disease in 38 patients subjected to the Paulino procedure.

Orleans. There was a preponderance of cases in the older age groups (figure 3). Fifty-five per cent of the patients were more than forty, and 23 per cent were more than fifty years of age. The four bilateral operations were performed in patients twenty-eight, thirty-eight, fifty-two, and fifty-six years of age. In 79 per cent, the disease was bilateral. Eighty-two per cent had far advanced tuberculosis, and 18 per cent had moderately advanced disease (figure 4). Although the lesions did not extend below the hilum, in almost every instance extensive cavitary disease was present. In 7 cases, active disease was also present in the dorsal segment of the lower lobe.

Bacteriology and chemotherapy: Early in the series, preoperative antimicrobial therapy was given only for special indications because prophylactic streptomycin therapy for thoracoplasty was considered unnecessary. The more recently operated patients received streptomycin and other antituberculous drugs. Fourteen received no drug therapy preoperatively, 8 received less than 30 gm. of streptomycin, 6 received between 30 and 60 gm., and 10 received more than 60 gm. Postoperatively, 3 patients received no streptomycin, 16 received less than 15 gm., 15 received between 15 and 30 gm., and in 8 more than 30 gm. were given.

In 28 patients, 11 of whom had received considerable antimicrobial therapy, the sputum was positive for tubercle bacilli at the time of the initial operation. In 10 cases, the sputum was negative for tubercle bacilli.

OBSERVATIONS

Complications

The procedure has proved to be remarkably free of serious complications in spite of the fact that it was frequently performed in the presence of active disease

TABLE 1

POSTOPERATIVE COMPLICATIONS FOLLOWING LUNG SUTURE WITH PARTIAL THORACOPLASTY
42 Operations

	CASES
Excessive extrapleural fluid	11
Intrapleural fluid	8
Subcutaneous emphysema	4
Infection of extrapleural space	2
Empyema	1
Pulmonary embolism*	1
Respiratory failure*	1
Horner's syndrome	1

* Case fatality.

(table 1). There has been no instance of bronchial fistula, of tuberculous infection of the pleural or extrapleural spaces, or of early postoperative activation of pulmonary disease. There has been no evidence of the soft cotton sutures cutting through the tissues, nor has there been any evidence of pulmonary necrosis. There are no post-ligation pathologic studies available to report. Unfortunately, permission for autopsy could not be obtained in the 3 fatal cases, and as yet no resections have been performed subsequent to the ligation procedure. There must be a considerable margin of safety between adequate collapse and dangerous interference with pulmonary vascularity. The forty-two operations have been performed by ten different operators, seven of whom were members of the resident staff.

Extrapleural fluid accumulated in all cases. It was aspirated if it seemed to interfere with respiration. Fluid accumulation was considered excessive if more than one aspiration was required. In 2 instances extrapleural fluid became infected with pyogenic organisms, but the infection responded to open drainage. The pleura was torn and intrapleural fluid accumulated in 8 cases. In one case a nontuberculous empyema developed, which also responded to simple open drainage. It is now believed that, if the pleura is torn, intercostal tube drainage should be instituted. One patient (*Case 1*) developed the only postoperative skeletal deformity, as a result of the scapula slipping inside the rib cage. Two postoperative and one late death will be discussed below.

Postoperative Pulmonary Function

The operation has been followed by a gratifying preservation of respiratory function. Preoperative and postoperative pulmonary function studies revealed a mean loss of 143 cc. in vital capacity in 13 cases of unilateral operation and a mean loss of 6 liters per minute in maximum breathing capacity in 9 cases of unilateral operation. All 3 patients who have survived a bilateral operation are free of significant clinical respiratory insufficiency. The function studies in 2 of these, previously reported (1), confirm the clinical impression.

The last case of a bilateral operation (*Case 38*) was a patient operated upon at two-week intervals in August, 1953, after prolonged antimicrobial therapy had

FIG. 5

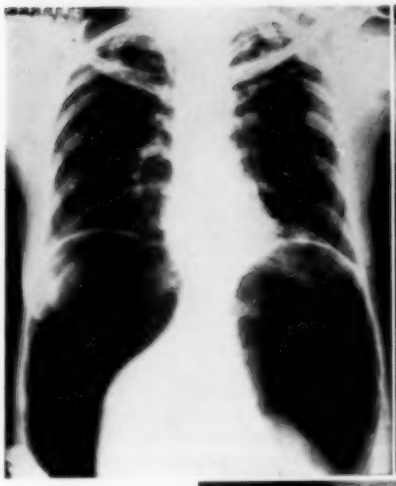

FIG. 6

FIG. 7

FIGS. 5, 6, and 7. *Case 38.* J. L., a 38-year-old female, with far advanced bilateral cavitary tuberculosis. Roentgenograms obtained prior to surgery, three days following operation on the left side, and one month following operation on the right side.

resulted in conversion of the sputum in spite of numerous residual bilateral cavities.

The preoperative and postoperative roentgenographic appearance of the chest are presented in figures 5, 6, and 7. Figure 6 demonstrates the early postoperative accumulation of extrapleural fluid, which absorbed without aspiration. Figures 8 and 9 demonstrate the lack of postoperative deformity.

FIG. 8 FIG. 9

FIGS. 8 and 9. *Case 38.* Photographs six weeks following surgery.

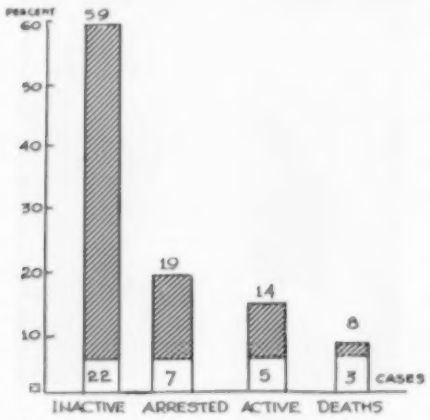

FIG. 10. Results three months or longer following Paulino procedure in 37 cases.

Postoperative Status of Tuberculosis

There have been 37 patients (forty operations) who have been followed long enough for an evaluation of the results of operation. In 22 (59 per cent), the tuberculosis has been classified as inactive[3] for a mean period of twenty-three months; in 7 (19 per cent), the lesions have been arrested for a mean period of eleven months. Five patients (14 per cent) have active disease, and 3 (8 per cent) are dead (figure 10). The only patient with arrested disease with occasionally "positive sputum" cultures (*Case 9*) is clinically well and working twenty months

[3] National Tuberculosis Association Classification of 1950 used throughout this report.

after bilateral operations for extensive cavitary disease. As no other surgical procedure could have been used in this case, the result was not a disappointment.

Of the 5 patients with persisting active disease, one (*Case 1*) is improved. The ipsilateral disease in this patient has remained inactive for four years after operation. A small contralateral lesion became active two years postoperatively and has not been completely controlled because the patient refuses to submit to further surgical therapy. *Case 19* represents a complete failure of the technique. It is the only instance in which the diseased tissues slipped down out of the ligatures, probably at operation. Conservative therapy of this patient has resulted in "sputum conversion," but a small contralateral cavity remains. *Case 23* represents an error in judgment. This patient had complete destruction of an upper lobe with fibrosis, atelectasis, and persistent cavitation. Several months after apparent postoperative arrest, active disease under the ligatures became evident and contralateral spread of disease occurred. Lobectomy would have been a preferable procedure in these circumstances. The patients of *Cases 29* and *34* both had extensive disease with cavities in the dorsal division of the lower lobe in addition to upper lobe disease which had failed to respond to intensive chemotherapy and bed rest. Resection or a more extensive thoracoplasty were contraindicated because of the limitations of the respiratory reserve. The pneumonolysis was carried below the hilum posteriorly and the lowest ligatures were placed on a bias. This maneuver was apparently successful in controlling 5 other similar cases, but the failure in these 2 cases (*Cases 29* and *34*) indicates the need for caution in pushing the indications for this operation so far.

Sudden death on the fourteenth postoperative day following the second procedure in one patient (*Case 12*) was thought to be due to massive pulmonary embolism. Another patient (*Case 8*) had very extensive bilateral disease and a very limited respiratory reserve. He died of respiratory failure on the eigth postoperative day. In retrospect, surgical therapy of any type was contraindicated in this case. The only late death (*Case 10*) occurred five months after surgery from massive pulmonary hemorrhage. A large, persistent, contralateral paramediastinal cavity became apparent immediately after surgery, and it was believed that the fatal hemorrhage occurred at this point. Thus, one death occurred as a surgical complication. The other 2 occurred because the cases were not suitable for any type of surgical therapy.

Approximately 80 per cent of the patients have experienced apparent arrest or inactivation of their disease following this procedure, and in only one case (*see Case 23* above) has ipsilateral disease, once apparently controlled, subsequently reactivated.

DISCUSSION

The present experience indicates that suture ligation of the lung with partial thoracoplasty is a relatively safe, reliable means of assisting in the control of properly selected advanced cases of pulmonary tuberculosis of the upper half of one or both lungs. It is a single-stage operation and may be used bilaterally. It causes minimal deformity and minimal loss of respiratory function.

TABLE 2

POSSIBLE ALTERNATIVE PROCEDURES (RESECTIONS) IN THE 38 CASES OF LUNG SUTURE WITH PARTIAL THORACOPLASTY

	CASES
Unilateral	
Segmental resection	2
Lobectomy or segmental resection	4
Lobectomy	13
Lobectomy and segmental resection	3
Bilateral	
Bilateral segmental resection	2
Bilateral lobectomy or segmental resection	2
Lobectomy and segmental resection	5
Bilateral lobectomy	2
Bilateral lobectomy and segmental resection	1
No alternative possible	4

TABLE 3

INDICATIONS FOR LUNG SUTURE WITH PARTIAL THORACOPLASTY IN 38 CASES

	CASES	PER CENT
General indications	13	34
Special indications	25	66
Possible bilateral operation	6	
Probable bilateral operation	11	
Marginal respiratory functional reserve	7	
Resection technically difficult or hazardous	4	

Evaluation of the relative merits of a given surgical procedure is difficult in the face of rapid developments in both the medical and surgical treatment of pulmonary tuberculosis. In the brief period of experience with the present procedure, the chief alternative procedure has changed from a more extensive thoracoplasty to pulmonary resection. In retrospect, resection of a lobe or segment might have been expected to remove the major foci of disease in 50 per cent of the cases in the present study. In the remainder, more extensive procedures would have been necessary (table 2).

The present procedure was chosen because of general indications for surgical therapy in 13 cases (34 per cent) and because of special indications for this particular operation in 25 cases (66 per cent) (table 3). A high percentage of the latter patients had bilateral disease which did, or might, require bilateral surgical therapy. Very extensive and hazardous resections would have been required in the 4 patients in whom bilateral operations were performed. The presence of a marginal respiratory reserve was considered a special indication for the procedure because of the relatively safe postoperative course and the minimal loss of respiratory function. Cases in which resectional therapy would have been particularly difficult or hazardous were considered indications for the present operation.

The above experience indicates that lung suture with partial thoracoplasty is superior to other types of partial thoracoplasty. No significant foreign material is introduced, no large empty space is created, and a reliable degree of collapse, compression, and fixation of the diseased lung is attained as the ligatures are carefully applied under direct vision. The controlled fixation, collapse, and compression are more effective than simply collapsing the diseased tissues down onto mobile, elastic, and active lung below the level of collapse.

When disease does not extend below the level of the hilum, the suture procedure is preferable to more extensive staged thoracoplasty techniques because: the former appears to be equally effective in the control of the disease; it is a single-stage operation; deformity and loss of respiratory function are minimal; and it may be applied to bilateral disease.

Resection of the involved tissues is theoretically preferable to collapse therapy as the major disease foci are completely removed. The ability of chemotherapy to arrest the activity of the disease prior to operation in many instances and the employment of careful techniques of lobectomy and segmental resection have greatly increased the scope and safety of resectional surgery for pulmonary tuberculosis. Under circumstances in which excisional surgery can be performed safely and adequately, it is probably the procedure of choice, but, when it promises to be hazardous or technically difficult, the Paulino procedure may be considered as a safe, effective alternative.

The persistence of tubercle bacilli in the sputum renders resection of less than an entire lobe a relatively hazardous procedure. Pleuritis not only renders surgical excision technically difficult, but it makes adequate expansion of the remaining lung problematic and may necessitate a concomitant partial thoracoplasty. Under these circumstances, the technically simpler and less hazardous Paulino procedure may be considered.

When other procedures are contraindicated, the Paulino procedure may be performed to include disease extending down into the superior portion of the lower lobe. Good results may be obtained, but the cases must be carefully selected. In the presence of extensive bilateral disease, each case must be carefully evaluated. In essence, the Paulino procedure may be effectively used in selected cases.

SUMMARY

A four-year experience with a technique of partial thoracoplasty and suture ligation of the lung indicates that it is a safe, reliable method of assisting in the control of pulmonary tuberculosis in properly selected cases of involvement of the upper half of one or both lungs. It is a single-stage operation in which costal resection and skeletal deformity are minimal and respiratory function is well preserved.

The present experience indicates that lung suture with partial thoracoplasty is more reliable and less complicated than other forms of partial thoracoplasty. For disease which does not extend below the hilum, the procedure has significant advantages over more extensive thoracoplasty techniques. Under certain circumstances it is preferable to excisional surgery and, in a few carefully selected cases,

lung suture may be used effectively when all other surgical techniques are contraindicated.

SUMARIO

Ligadura-Sutura del Pulmón y Toracoplastia Parcial en el Tratamiento de la Tuberculosis: Cuatro Años de Observación

Cuatro años de observación de una técnica de toracoplastia parcial y ligadura-sutura del pulmón indican que se trata de un método inocuo y seguro para ayudar a dominar la tuberculosis pulmonar en casos debidamente escogidos de invasión de la porción superior de uno o de ambos pulmones. Es una operación en un tiempo en la que hay un mínimo de resección costal y de deformidad esquelética y se resguarda bien la función respiratoria.

La experiencia de los AA. indica que este procedimiento es más eficaz y menos complicado que otras formas de toracoplastia parcial. Para la enfermedad que no se extiende más abajo del hilio, el método posee ventajas importantes sobre técnicas más extensas de toracoplastia. En ciertas circunstancias, es preferible a la excisión quirúrgica, y en algunos casos escogidos cuidadosamente puede usarse eficazmente cuando están contraindicadas todas las demás técnicas quirúrgicas.

RESUME

Ligature du poumon par suture et thoracoplastie partielle dans le traitement de la tuberculose: Une expérimentation de quatre années

Quatre années d'expérimentation de la thoracoplastie partielle avec ligature du poumon par suture indiquent la valeur et la sécurité de cette méthode, qui permet de juguler la tuberculose pulmonaire dans certains cas sélectionnés avec présence de lésions intéressant la moitié supérieure de l'un ou des deux poumons. C'est une opération en un temps dans laquelle la résection costale et la déformation du squelette sont réduites au minimum et la fonction respiratoire bien conservée.

L'expérience acquise par les auteurs indique que cette méthode est plus sûre et moins compliquée que les autres procédés de thoracoplastie partielle. Quand il s'agit de lésions qui ne s'étendent pas au-dessous du hile, le procédé présente des avantages appréciables sur les thoracoplasties plus extensives. Dans certaines circonstances, elle est préférable à l'exérèse et, dans quelques cas soigneusement choisis, elle peut se montrer très efficace quand toutes les autres techniques chirurgicales sont contre-indiquées.

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THE COMPARISON OF SOME TUBERCULINS IN BCG-VACCINATED AND UNVACCINATED PERSONS[1, 2]

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INTRODUCTION

The tuberculin test has proved a valuable aid in the diagnosis of tuberculosis, in case finding, in determining the epidemiology of this disease, in differentiating pulmonary lesions of viral or mycotic etiology from tuberculosis, and in indicating a successful vaccination with BCG vaccine.

With the significant decrease in recent years in the morbidity and mortality from tuberculosis in the general population, a significant decrease has occurred, especially in the younger age groups, not only in the per cent who react to tuberculin but also in the intensity of the local reaction. Because of this decrease in the level of tuberculin hypersensitivity, it is essential to use tuberculin of high potency to detect those with a low level of hypersensitivity and to reduce the number showing atypical or doubtful reactions.

It is possible that the use of less potent tuberculin may be adequate for diagnostic clinical purposes. It has been shown by Hetherington, McPhedran, Landis, and Opie (1), Wells and Smith (2), Aronson and Aronson (3), and by others that significant pulmonary lesions of tuberculosis found on roentgenographic examination are usually associated with a high level of tuberculin sensitivity and that patients with such lesions usually react definitely to the initial small dose of tuberculin.

A variety of tuberculins have been advocated since the original description of the preparations of Old Tuberculin by Koch (4). With but few exceptions, these tuberculins have not withstood the test of time, and Old Tuberculin continues to have its advocates. The main objections to the use of Old Tuberculin are the variations in the potency of different samples and the presence of inert substances, such as salts, glycerin, peptone, and some metabolites of the tubercle bacilli. Attempts to purify and isolate the active principle of Old Tuberculin were originally made by Koch (4), who precipitated the protein fraction from Old Tuberculin with alcohol. In more recent years, Seibert and Munday (5) and Seibert (6) have isolated the protein fraction responsible for the tuberculin reaction. They found that the potency of tuberculin was related to the tuberculoprotein of the bacillus.

The potency of tuberculin cannot be determined by chemical or serologic methods. The specific biologic activity of tuberculin for diagnostic purposes is best measured by its local cutaneous effect on tuberculous guinea pigs rather

[1] From Henry Phipps Institute, University of Pennsylvania; and the Bureau of Tuberculosis Control, Commonwealth of Pennsylvania, Harrisburg, Pennsylvania.

[2] Presented before the Epidemiology and Laboratory Sections, American Public Health Association, at the Eighty-First Annual Meeting in New York, November 13, 1953.

than by the induction of tuberculin shock on such animals as shown by Eagleton and Baxter (7), Aronson (8), Calmette and DePotter (9), and Okell and Parish (10).

With the introduction of BCG vaccine as an immunizing agent against tuberculosis, the use of tuberculin assumed another important role. For want of a better measure, the tuberculin reaction has been used as an index of a successful vaccination on the basis of the conversion of a negative pre-vaccinal tuberculin reaction to positive. Furthermore, the immunogenic property of different samples of BCG vaccine can be evaluated on the basis of the per cent of vaccinated persons who develop a post-vaccinal tuberculin reaction.

At the present time, Old Tuberculin (OT) and purified tuberculin are used widely.

Old Tuberculin is prepared, with but slight modification, in the same manner as originally prescribed by Koch (4). One or more strains of tubercle bacilli are grown for six to nine weeks on glycerol veal or beef infusion broth. The cultures are first sterilized by flowing steam, the bacillary bodies are removed by filtration, and the filtrate is then concentrated on a water bath to one-tenth of its original volume. This concentrated material is then filtered through bacterial-proof filters and constitutes Old Tuberculin.

The procedures used by different investigators to obtain purified tuberculin vary in some details, resulting in corresponding differences in degree of purity, sensitivity, and potency of different preparations of purified tuberculin. The modes of preparation of the different purified tuberculins are reviewed.

The original purified protein derivative (PPD) was prepared according to Seibert (6) by growing cultures of tubercle bacilli on Bureau of Animal Industry (BAI) synthetic culture medium. When these cultures had reached their maximum growth, they were sterilized by a three-hour exposure to flowing steam. The bacillary bodies were removed by filtration, and the filtrate was concentrated on a water bath to one-fifth of its original volume. The concentrated filtrate was diluted with 0.5 per cent phenol and then concentrated by ultrafiltration through an alumdum shell impregnated with 13 per cent gun cotton dissolved in acetic acid. The concentrated residue was filtered through a bacterial-proof filter and the protein fraction was precipitated by the addition of a sufficient amount of 50 per cent trichloracetic acid to give a final concentration of 10 per cent trichloracetic acid. The precipitated protein was collected, washed with 10 per cent trichloracetic acid, dried *in vacuo*, washed repeatedly with ether, and dried. The dried powder constituted the original purified protein derivative (PPD). This original PPD was utilized in studies until 1941, when it was no longer available.

The purified tuberculin, designated as *renset tuberkulin* (RT) or *purified tuberculin* (PT), prepared at the State Serum Institute, Copenhagen, Denmark, differs in some respects from that recommended by Seibert (6). According to Jensen and associates (11) and Lind (12), the cultures were grown on Sauton medium and sterilized by flowing steam. The cultures were then filtered through a bacterial-proof filter and the filtrate was concentrated by ultrafiltration through 7 per cent collodion membranes. The purified protein was precipitated with 2 per cent trichloracetic acid and the precipitate washed with ether and dried. This purified tuberculin has been used

extensively in various parts of the world by the members of the International Tuberculosis Campaign, an organization consisting of UNICEF and some Scandinavian voluntary groups.

The *Weybridge PPD* was prepared at the Veterinary Laboratory of the Ministry of Agriculture and Fisheries, Weybridge, Surrey, England. The details of the method of preparation have been described by Green (13). The preparation of the Weybridge PPD differs from the original method of Seibert (6) in that the culture filtrate is not concentrated by ultrafiltration and the protein is precipitated by the addition of 50 per cent trichloracetic acid to give a final concentration of 4 per cent to the unconcentrated culture filtrate. The precipitate is washed repeatedly with trichloracetic acid, followed by washing with acetone and ether. The purified tuberculin is then dried and the powder dissolved as required.

When studies by physicochemical methods indicated that the trichloracetic acid purified protein derivative contained a significant per cent of nucleic acid and carbohydrates, Seibert and Glenn (14) modified the original procedure by growing the culture on Long's synthetic medium, eliminating the preliminary concentration of the filtrate by heat and, instead, concentrating the filtrate in the cold by ultrafiltration. The protein was isolated from this concentrated filtrate by repeated precipitation with neutralized saturated solution of ammonium sulfate. The precipitate was then washed free of ammonium sulfate, filtered through a bacterial-proof filter, and preserved by freeze-drying. The tuberculin obtained by this method was designated as *Standard Purified Protein Derivative*, or PPD-S. This preparation proved to be twice as potent as the original trichloracetic acid derivative. Unlike the original PPD, Seibert and Glenn (14) found that PPD-S was antigenic, as evidenced by the production of precipitins in rabbits injected repeatedly with this preparation and by its ability to induce an Arthus phenomenon in these animals, although repeated injections of ten times the regular second dose used in the skin test in man did not lead to significant sensitization in guinea pigs.

The variety of tuberculins and the different techniques which have been recommended have given rise to some confusion. In order to evaluate the different tuberculins now in use and to determine the relative sensitivity of the intracutaneous and patch tests, the present writers have carried out a series of comparative tests with the different tuberculins among both nonvaccinated and BCG-vaccinated persons.

PLAN OF INVESTIGATION

Procedure

The relative value of the different tuberculins was determined by conducting simultaneous tests, using the recommended dose for each preparation. The different samples of tuberculin were diluted immediately preceding the test with either physiologic saline buffered with phosphate to give pH 7.2 or, in the case of tablets, with the diluent supplied with the tablets. All of the diluted samples of tuberculin were used within ten to twelve hours after preparation. The glassware used in diluting the tuberculins and all syringes with but few exceptions were new and were marked conspicuously with different colored tape for each preparation. Occasionally, when it became necessary to use the same syringes for different samples, the syringes were washed well, soaked for two to three days in sulfuric acid bichromate cleaning fluid, and washed free of acid before they were used.

The various tuberculins were injected intracutaneously in a total quantity of 0.1 ml. by

means of a 1.0 ml. tuberculin syringe and a 26-gauge platinum needle. The two tuberculins which were compared were injected simultaneously as superficially as possible in the skin of the upper third of the volar surface of the forearms. The results were read forty-eight hours later by the same personnel and were graded according to the extent of edema as outlined by Aronson (15). In order to minimize any bias in the interpretation of the different tuberculins, they were coded by letter and the injections of the different tuberculins were changed from one forearm to the other from time to time.

Interpretation of Tuberculin Reaction

It is difficult to measure with any degree of accuracy the exact limits of a reaction to tuberculin. The central area of induration, which is usually well defined, merges into a less well-defined area of edema which in turn gradually blends into the surrounding reddened skin. The character of the tuberculin reaction depends, not only upon the intensity of exposure to tubercle bacilli, but also upon the level of hypersensitivity of the person and the nature of the cutaneous and subcutaneous tissue. In infants the local reaction to tuberculin is usually characterized by a sharply defined dense area of induration surrounded by a localized area of firm edema. On the other hand, among the aged—and especially among those whose skin is thin and parchment-like—not only is the level of hypersensitivity low, but the local reaction is characterized by a diffuse, deep red blush which persists for days, associated with but slight or no palpable edema. Among those with abundant loose, soft, subcutaneous tissue, the local reaction is usually characterized by a diffuse, ill-defined area of edema, difficult to palpate. In a relatively small per cent of patients with well-developed muscles in the forearm, the writers have observed a dense, sharply localized, elevated area of induration with no significant zone of edema. Occasionally, a sharply defined vesicle, 4 to 6 mm. in diameter, containing clear, pale yellowish fluid with no surrounding inflammatory area has been observed. Severe reactions to tuberculin may be associated with a vesicle of varying size filled with clear yellowish fluid and extensive edema, by a definite central area of necrosis in the center of the indurated area, or by lymphangitis extending upward on the anterior or internal margin of the arm. Severe local reactions may be associated with indefinite symptoms of a general reaction characterized by slight fever, headache, and muscular pains.

The criterion used for a positive tuberculin reaction has been a local inflammatory reaction associated with an area of palpable induration or edema measuring 5 mm. or more in diameter. The writers have been impressed, however, by the frequent appearance of redness with slight or no palpable edema following the injection of the different tuberculins in those who have previously received BCG vaccine. This reaction, it is believed, is specific, since these persons originally failed to react to the same or larger dose of tuberculin just before or at the time they received BCG vaccine. They also failed to show any evidence of local hypersensitivity (Koch phenomenon) following BCG vaccination. The intensity of this type of reaction is not significantly increased by increasing the dose of tuberculin.

Because of the high level of hypersensitivity which may be encountered among the general population, and especially in those areas with a high morbidity and mortality from tuberculosis, it is advisable to use a small initial dose of the different tuberculins. This is especially true for those persons who have extrapulmonary tuberculosis or primary lesions of pulmonary tuberculosis. On the other hand, hypersensitivity is usually low in those suffering from miliary tuberculosis, from far advanced tuberculosis, following BCG vaccination, and from certain intercurrent exanthemata.

To obviate as much as possible the severe reactions to tuberculin, an initial dose of 0.01 mg. of OT and either 0.00001 or 0.00002 mg. of the purified forms of tuberculin has been used throughout the studies among the general population.

Because of the difference in the level of tuberculin hypersensitivity and the character of the local reaction to tuberculin among those who have undergone a natural infection with virulent tubercle bacilli, compared with those who have developed hypersensitivity

following the administration of BCG vaccine, this study has been divided into two parts. The first deals with the comparison of different tuberculins among unvaccinated persons; and the second, with a comparison of different tuberculins among those who had previously received BCG vaccine. The members of both groups consist of persons who, with but few exceptions, were inmates of correctional or mental institutions.

OBSERVATIONS

Comparative Potency of Different Samples of Old Tuberculin

That different samples of OT may vary in their potency is well recognized. Aronson (8), who determined the relative potency of 10 different samples of OT by intracutaneous titration on tuberculous guinea pigs and tuberculous goats, found that these samples varied widely. In recent years, the present writers have compared several samples of OT from a manufacturer who has supplied them with OT over the past twenty-five years with a sample of OT from a second manufacturer. The results of these comparative tests made on unvaccinated adults are presented in table 1.

It will be noted from table 1 that not only are there differences in the potency of sample "A" as compared with sample 530, prepared by a different manufacturer, but there are also significant differences in samples 284 and 547 and samples 284 and 550, all of which were prepared by the same manufacturer. On the other hand, samples 416 and 550 of OT, also prepared by the same manufacturer, are of comparable potency. These variations are reflected, not only by differences in the per cent who react, but also by differences in the intensity of the local reactions.

The relative stability of OT is indicated by the fact that sample 284, prepared approximately twenty-five years ago and stored at room temperature during this time, continues to show a high level of potency.

TABLE 1

COMPARISON OF DIFFERENT SAMPLES OF OLD TUBERCULIN ON UNVACCINATED PERSONS

SAMPLES OF OT	NUMBER TESTED	POSITIVE TO 0.01 MG. OT		NUMBER AND DEGREE OF REACTION				
		Number	Per Cent	1+	2+	3+	4+	Doubtful
Lot 530	157	131	83.4	9	82	38	2	7
Lot "A"	157	101	64.3	27	63	10	1	12
Lot 284	230	163	70.9	19	115	23	6	47
Lot 547	230	204	88.7	4	110	87	3	15
Lot 284	164	133	81.1	5	93	34	1	27
Lot 550	164	157	95.7	1	49	98	9	5
Lot 416	202	170	84.2	7	111	50	2	15
Lot 550	202	177	87.6	1	89	86	1	12
Untreated Lot 530	56	43	76.8	2	18	22	1	4
Freeze-dried Lot 530	56	35	62.5	11	20	4	0	3
Lot "A"	60	37	61.7	8	26	3	0	8
Freeze-dried Lot 530	60	36	60.0	8	20	8	0	5

The practicability of the freeze-drying process as a method of distribution and preservation of small amounts of OT was investigated. Varying dilutions of sample 530 OT were freeze-dried by the manufacturer and were regenerated with sterile distilled water just prior to being used. The potency of the freeze-dried OT was compared in the same persons with the untreated sample 530 OT as well as with sample "A" OT. The results of this study, presented in table 1, show that freeze-drying OT results in a loss of potency, as indicated not only by the smaller per cent who react to the freeze-dried sample but also in the smaller number of 3-plus reactions. Further proof of the effect of freeze-drying on OT is indicated by the fact that, while the untreated sample 530 OT is significantly more potent than sample "A", nevertheless, after freeze-drying, its potency is comparable to that of the weaker sample "A" OT.

The decrease in the potency of OT following freeze-drying was unexpected, especially in view of the drastic treatment of preparing OT by concentrating the culture filtrate by heat. One possible explanation is that the decrease in potency might be due to the loss of small amounts of the tuberculin during freeze-drying. This explanation is suggested by the studies of Stein and Rogers (16), who found that viable bacilli and viruses are carried over to the condenser during freeze-drying of bacterial cultures and samples of viruses. The present writers have repeated these studies with cultures of *S. marcescens* and have recovered large numbers of this organism from the previously sterilized manifold and condenser. In addition, samples of phosphate buffer solution containing P^{32} as a tracer were freeze-dried. By means of a Geiger-Muller tube and scaler, the transfer of P^{32} was followed from the vials of buffer solution through the manifold into the condenser.

Comparative Potency of Preparations of Purified Protein Tuberculins

The purified protein tuberculin preparations now available represent fractions prepared by precipitating tuberculoprotein with either trichloracetic acid or ammonium sulfate.

The designation *PPD* has unfortunately been used interchangeably for both the trichloracetic acid and the ammonium sulfate purified protein derivative. It is, therefore, difficult to determine from the literature, in some cases, which preparation of tuberculoprotein has been used. Since the ammonium sulfate preparation PPD-S was not on the market until 1942, it is fair to assume that studies antedating that year deal with the trichloracetic acid preparation.

As the original sample of PPD prepared and supplied by Seibert (6) was no longer available at the time of the present study, it was not possible to compare the relative potency of this sample of PPD with that of PPD-S, also prepared by Seibert and Glenn (14). Such a comparison had been conducted, however, by Aronson and Parr (17) in 1940 on a group of 870 Indian children of school age who had not received BCG vaccine. The children were injected intracutaneously with 0.00002 mg. of PPD and with 0.00001 mg. of PPD-S.

The results observed at that time, which are presented in table 2, indicate a close agreement both in the per cent who reacted to both tuberculins and in the degree of reaction. When those who failed to react to the initial test were retested

with 0.005 mg. of PPD and 0.0025 mg. of PPD-S, 7.6 and 13.0 per cent reacted to PPD and PPD-S, respectively. During the course of this study, it was noted that, in general, the local reaction to PPD-S was diffuse, ill-defined, and more difficult to interpret than the local reaction following the injection of either OT or PPD. These studies were extended to include two samples of trichloracetic acid purified tuberculin. One, RT or PT Lot XXII, was prepared at the State Serum Institute, Copenhagen, and kindly supplied by Dr. K. Tolderlund; while the other, *Weybridge PPD*, was prepared at the Veterinary Laboratory, Weybridge, Surrey, England, and kindly supplied by Mr. A.B. Paterson. These two samples of purified tuberculin were compared with a sample of PPD-S supplied by Dr. Carroll E. Palmer, U. S. Public Health Service. The comparative tests were carried out simultaneously in mental institutions on groups of adult patients, none of whom had previously received BCG vaccine. An initial dose of 0.00002 mg. was used for the three different preparations of purified tuberculin. The results of these comparative tests, all of which were made and interpreted by the same personnel, are summarized in table 2.

The data presented in table 2 indicate that in the 1940 study the original preparations of PPD and PPD-S, both of which were obtained from Dr. Seibert, were comparable in potency. The observations made during the present study indicate, that, while the per cent of reactors to RT or PT XXII of the State Serum Institute, Copenhagen, was approximately the same as to the PPD-S of the U. S. Public Health Service, the number of well-marked reactions was greater with the PPD-S.

The sample of Weybridge PPD appeared somewhat more potent than the sample of PPD-S on the basis of the greater number of 3-plus reactions. The samples of PPD-S obtained from the U. S. Public Health Service and the PPD-S obtained from Dr. Seibert showed no significant differences in potency. These

TABLE 2

COMPARISON OF DIFFERENT PURIFIED TUBERCULINS ON UNVACCINATED PERSONS

SAMPLES OF PURIFIED TUBERCULIN	DOSE OF TUBERCULIN (MG.)	NUMBER TESTED	POSITIVE		DEGREE OF REACTION				
			Number	Per Cent	1+	2+	3+	4+	Doubtful
PPD Phipps	0.00002	870	464	53.3	11	152	301	0	9
PPD-S Phipps	0.00001	870	468	53.8	14	171	283	0	9
PPD-S U.S.P.H.	0.00002	316	254	80.4	36	166	49	3	41
RT Lot XXII	1 TU*	316	237	75.0	92	129	16	0	52
PPD-S U.S.P.H.	0.00002	140	84	60.0	8	60	16	0	13
Weybridge PPD	0.00002	140	92	65.7	4	53	35	0	14
PPD-S U.S.P.H.	0.00002	222	147	66.2	15	90	39	3	39
PPD-S Phipps	0.00002	222	143	64.4	20	81	31	2	29
PPD-S Phipps	0.00002	208	130	62.5	21	85	21	3	25
PPD-S Tablets "B"	0.00002	208	113	54.3	36	65	9	3	27
PPD-S Phipps	0.00002	180	127	70.6	18	84	24	1	24
PPD-S Tablets "C"	0.00002	180	73	40.6	23	43	7	0	44

* One TU equals 0.000013 mg. of purified tuberculin.

results indicate that different preparations of purified tuberculin, like OT, may vary in their potency.

Because the potency of diluted tuberculin decreases after several days, it is necessary to prepare fresh dilutions as required. Since this is often inconvenient, time-consuming, and wasteful, Reichel and Clark (18) described a method of preparing sterile tablets with the desired amount of PPD-S incorporated in Beta-lactose. These tablets are supplied with sufficient diluent to give the desired dose. The potency of first-dose tablets, in which 0.1 ml. of the dissolved tablet is equivalent to 0.00002 mg. of PPD-S, was compared in a group of adults with a sample of the standard PPD-S. The results of comparative tests, which are presented in table 2, indicate that the tablets of PPD-S prepared by companies "B" and "C" differed in potency from that of the standard PPD-S. The PPD-S tablets prepared by company "B" gave 8.2 per cent fewer reactions and fewer strong 3-plus reactions than those obtained with standard PPD-S. The tablets prepared by company "C" showed 30 per cent fewer reactions, fewer 2- and 3-plus reactions, and a higher number of doubtful reactions than were observed following the injection of the standard PPD-S.

Comparison of OT and Purified Tuberculin

There are but few published data comparing the sensitivity of different purified tuberculins with that of OT, either among the unvaccinated population or following BCG vaccination.

Long, Aronson, and Seibert (19) found that the incidence of reactions in man to 0.00002 mg. of PPD was comparable to that obtained with 0.01 mg. of OT (a commercial sample) both in the per cent of those who reacted and in the intensity of the reaction. On the basis of these observations, a dose of 0.00002 mg. of PPD was recommended as the initial dose. With the larger doses, however, a higher per cent reacted to 0.005 mg. of PPD than to 1.0 mg. of OT.

Plunkett and Siegal (20) found that, of 1,747 persons tested with OT and PPD, 44.5 and 18.0 per cent reacted to 0.00002 mg. of PPD and 0.004 mg. of OT, respectively. When those who failed to react were retested with 0.0005 mg. of PPD and 0.1 mg. of OT, 56.9 and 54.2 per cent reacted to the PPD and OT, respectively. When doses of 0.005 mg. of PPD and 1.0 mg. of OT were used, 61.2 and 60.4 per cent reacted to PPD and OT, respectively. The cumulative results for the three tests were 61.2 and 60.4 per cent for the PPD and OT, respectively. Savage (21) tested 437 Negroes between the ages of twelve and twenty-four years with two different samples of OT, PPD, and the patch test. He noted a marked variation in the reaction of the group to the different tuberculins. With OT, 42.8 and 41.9 per cent reacted to 0.01 mg. of OT, samples "A" and "B", respectively, while 20.2 per cent reacted to 0.00002 mg. of PPD. To the second dose of 1.0 mg. of OT and 0.005 mg. of PPD, 17.2 and 5.7 per cent reacted to samples "A" and "B" of OT, respectively, while 26.4 per cent reacted to the PPD.

In 1940, Aronson and Parr (17) found that, of 404 Indian children of school age tested simultaneously with 0.01 mg. of OT and 0.00002 mg. of PPD, 42.1 and

TABLE 3

COMPARISON OF OLD TUBERCULIN AND PURIFIED TUBERCULINS IN UNVACCINATED PERSONS

DESIGNATION OF TUBERCULIN	DOSE OF TUBERCULIN (MG.)	NUMBER TESTED	POSITIVE		DEGREE OF REACTION				
			Number	Per Cent	1+	2+	3+	4+	Doubtful
OT 416	0.01	404	170	42.1	1	58	111	0	0
PPD Phipps	0.00002	404	169	41.8	2	56	111	0	0
OT 416	0.01	495	419	84.6	2	137	280	0	5
PPD-S Phipps	0.00001	495	419	84.6	6	109	304	0	3
OT 530	0.01	177	139	78.5	6	79	52	2	6
PPD-S Phipps	0.00001	177	110	62.1	44	58	7	1	12
OT 550	0.01	243	183	75.3	7	94	80	2	29
PPD-S Phipps	0.00002	243	167	68.7	13	104	50	0	34
OT 550	0.01	817	531	65.0	32	290	207	2	22
RT Lot XXII	1 TU*	817	457	56.0	73	263	121	0	55
OT 550	0.01	802	569	71.0	23	297	247	2	20
Weybridge PPD	0.00002	802	507	63.2	73	299	133	2	40
OT "A"	0.01	56	32	57.1	20	9	2	1	8
PPD-S Phipps	0.00001	56	37	66.1	9	22	5	1	5
OT 550	0.01	556	397	71.4	16	169	209	3	23
PPD-S Tablet "B"	0.00002	556	321	57.7	40	215	66	0	42
OT 550	0.01	493	315	63.9	21	174	118	2	25
PPD-S Tablet "C"	0.00002	493	195	39.6	44	123	28	0	64
OT "A"	0.01	59	38	64.4	7	28	3	0	8
PPD-S Tablet "B"	0.00002	59	38	64.4	8	23	7	0	6

* One TU equals 0.000013 mg. of purified tuberculin.

41.8 per cent reacted to OT and PPD, respectively. Of another 495 Indian children tested simultaneously with 0.01 mg. of OT and 0.00001 mg. of PPD-S, 84.6 per cent reacted to both tuberculins.

Recently these studies were extended to include additional samples of OT and different preparations of purified tuberculin, both the standard solution from Dr. Seibert and tablets. These studies have been conducted on adult inmates of correctional or mental institutions, and the injections and interpretations were made by the same personnel. The results of the earlier studies and the present studies are presented in table 3.

The data presented in table 3 indicate that OT 416, PPD, and PPD-S are comparable in potency on the basis of the per cent who reacted to the initial dose and the intensity of the reactions. A higher potency of OT samples 530 and 550 over the samples of purified tuberculin is indicated by the somewhat higher per cent of reactors and the larger number of reactions in which the area of edema exceeded 20 mm. in diameter (3-plus). When OT 550 is compared with the three different purified tuberculins, it will be noted that 6.6, 9.0, and 7.8 per cent more reacted to OT 550 than to PPD-S, RT, or PT Lot XXII or Weybridge PPD, respectively. On the other hand, the lower potency of OT sample "A" was confirmed by the fact that 9.0 per cent more of the persons tested reacted to PPD-

S than to OT sample "A", and the degree of reaction was less marked with OT "A" than with PPD-S.

It was previously indicated in table 2 that the tablets of PPD-S, and particularly PPD-S tablets sample "C", were less potent than the non-tablet form of the standard PPD-S. These observations are confirmed by the data presented in table 3. Of the 556 persons tested simultaneously with 0.00002 mg. of PPD-S tablets, sample "B", and with 0.01 mg. of OT 550, 13.7 per cent more reacted to the OT than to the PPD-S tablets. Of the 493 persons tested with both 0.00002 mg. of PPD-S tablets sample "C" and 0.01 mg. of OT 550, 24.3 per cent more reacted to the OT than to sample "C" tablets. The OT gave a significantly larger number of 3-plus reactions than did the sample "C" tablets. The low potency of OT sample "A" is further indicated by the fact that its potency was comparable to PPD-S tablet "B", a preparation less potent than OT 550 or the standard PPD-S.

Comparison of the Intracutaneous and Patch Tests

To simplify the tuberculin test, Vollmer and Goldberger (22) recommended the application of Old Tuberculin to the cleansed unbroken skin by means of a patch of absorbent material impregnated with concentrated Old Tuberculin. These investigators found this method somewhat more sensitive than the Pirquet test. When the patch test was compared with the intracutaneous test using PPD, they found (23) that, of 169 tuberculous children tested, only one child who subsequently reacted to 0.005 mg. of PPD failed to react to the patch test. Krug and Glenn (24) found that, of 2,152 college students tested with both the intracutaneous test and the patch test, 22.1 per cent reacted to 0.00002 and 0.005 mg. of PPD-S, and 20.2 per cent reacted to the patch test.

The present writers have compared the relative sensitivity of the patch test and the intracutaneous method on a group of unvaccinated adults. The patch test was carried out by cleansing the skin between the scapulae with carbon tetrachloride, permitting the skin to dry, and applying the patch as firmly as possible to the cleansed skin. The patch was removed after forty-eight hours, and the reaction was read forty-eight hours after the removal of the patch.

Of 88 adults tested simultaneously with the patch test and the intracutaneous injection of PPD-S, 50.3 per cent reacted to the patch test and 65.2 per cent to the intracutaneous injection of 0.00001 mg. of PPD-S.

To further evaluate the relative merits of the two procedures, the manufacturers kindly made available a sample of the OT used in preparing the patch test. Of 84 persons tested simultaneously with the patch test and the intracutaneous injection of 0.01 mg. of the sample of OT used in preparing the patch test, 48.9 per cent reacted to the patch test and 63.0 per cent to the intracutaneous test.

Savage (21), who compared the patch test with the intracutaneous test, found that, while 39.8 per cent of 437 persons reacted to the patch test, a total of 60.0 and 46.5 per cent reacted to the intracutaneous test with 0.01 and 1.0 mg. of samples of OT which he designated as "A" and "B" and a total of 47.6 per cent reacted to 0.00002 and 0.005 mg. of PPD.

Relative Sensitivity of Tuberculins in BCG-Vaccinated Persons

The studies reported thus far have dealt with comparisons of different tuberculins on unvaccinated persons. Of the definite reactions among this population, a high per cent were in response to the initial small dose of either OT or purified tuberculin, indicating a high level of hypersensitivity. Groups with such high levels of hypersensitivity, resulting from repeated natural infection with virulent tubercle bacilli, are not as favorable for determining differences in the potency of tuberculins as groups with a lower level of sensitivity.

The parenteral administration of BCG vaccine in tuberculin-negative persons results in a low level of tuberculin sensitivity. Because of this, it is important that highly potent OT or purified tuberculin having a high specificity and sensitivity be used both in the selection of persons for BCG vaccination and for the post-vaccinal tuberculin test.

Aronson and McGettigan (25) found that 1.6 per cent of 2,655 persons who were negative to 0.01 and 0.1 mg. of OT showed a definite local, acute, painful, specific inflammation (Koch phenomenon) at the site of BCG vaccination. In 5.9 per cent, a less severe local inflammatory reaction was noted, while 92.5 per cent who were tuberculin-negative showed only a small sharply defined painless nodule at the site of BCG vaccination. On the other hand, of 193 persons who were negative to 0.01 mg. of OT but positive to 0.1 mg. of OT, 63.8 per cent showed a well-marked Koch phenomenon associated with pain; and 18.1 per cent, a somewhat less severe inflammatory reaction at the site of the BCG vaccination.

A further evaluation of the different samples of both OT and purified tuberculins was made on persons who had received BCG vaccine and who subsequently developed a low level of tuberculin sensitivity. The routine procedure which was followed in the use of BCG vaccine was to administer an initial intracutaneous injection of 0.01 mg. of OT. If after forty-eight hours there was a definite reaction to the OT, no further injections were made. If, on the other hand, the reaction was doubtful or if the area of edema measured less than 10 mm. in diameter, a second dose of 0.1 mg. of OT was administered. If after forty-eight hours the second test was negative or doubtful, BCG vaccine was then administered.

If the reaction to 0.01 mg. of OT was definitely negative, however, the person was then reinjected with 0.1 mg. of OT in the skin of the opposite arm and at the same time was injected intracutaneously, as superficially as possible, with 0.1 mg. of BCG vaccine into the skin overlying the deltoid region. The local reaction to both the second dose of 0.1 mg. of OT and to the BCG vaccine was observed forty-eight hours later in order to establish whether or not hypersensitivity to OT or to the BCG vaccine was present.

The potency of the different Old Tuberculins was determined by the simultaneous intracutaneous injections of paired tuberculins in different forearms of persons who had received BCG vaccine from two months to four years previously. The results of these comparative tests are summarized in table 4.

The relatively low percentage of positive reactions and the large number of doubtful or atypical reactions to 0.01 mg. of OT is indicative of the low level of

TABLE 4

COMPARISON OF DIFFERENT SAMPLES OF OLD TUBERCULIN ON BCG-VACCINATED PERSONS

SAMPLES OF OT	POST-VACCINAL INTERVAL	DOSE	NUMBER TESTED	POSITIVE		DEGREE OF REACTION				
				Number	Per Cent	1+	2+	3+	4+	Doubtful
		mg.								
Lot 284	1–3 years	0.01	264	52	19.7	5	47	0	0	158
Lot 547		0.01	264	100	37.9	14	83	3	0	134
Lot 284	1–3 years	0.01	188	64	34.0	9	54	1	0	84
Lot 550		0.01	188	115	61.2	7	88	19	1	65
Untreated Lot 530	2–3 months	0.1	463	459	99.1	21	334	104	0	3
Freeze-dried Lot 530		0.1	463	381	82.3	55	290	36	0	74

hypersensitivity induced by BCG vaccine. The differences in the potency of OT 284 and 547 and 284 and 550 are brought out more strikingly in the BCG-vaccinated persons than among the general population (table 1).

It will be noted that, of those tested with an initial dose of 0.1 mg. of untreated OT 530, only a small number of the vaccinated persons failed to react. On the other hand, of those tested with the freeze-dried sample of the same tuberculin, not only was the incidence of positive reactors smaller, but there were fewer definite reactions and a large number of doubtful or atypical reactions.

Because of the lower level of tuberculin hypersensitivity which follows BCG vaccination, 0.1 mg. of OT was used routinely as the initial post-vaccinal dose. The dose was not increased to 1.0 mg. in those who failed to react to 0.1 mg. of OT, since some of the reactions to the larger dose of OT may be nonspecific in nature.

As the level of tuberculin hypersensitivity following BCG vaccination decreases with increasing time, the observations on the comparative value of the different tuberculins were divided into a group which was tuberculin-tested two to five months after vaccination and a second group which was tested six months to four years after vaccination. The results of the different paired tests are presented in table 5 according to the dose of tuberculin and the degree of reaction.

From the data presented in table 5, it is evident that, among those vaccinated two to three months previously with different lots of BCG vaccine, a significantly higher per cent reacted to 0.1 mg. of OT 550 than to 0.0001 mg. of PPD-S or PPD-S tablets. Not only was the per cent of reactors to OT higher, but the number who showed a 2-plus or 3-plus reaction was higher and the number of doubtful or atypical reactions was smaller. On the other hand, the per cent of reactors and the degree of reaction were approximately the same with RT or PT XXII of the State Serum Institute, Copenhagen, or with Weybridge PPD as with OT. A comparison of RT or PT XXII and Weybridge PPD with PPD-S indicates that the incidence of reactors was higher and the intensity of the tuberculin reaction was more marked with RT or PT XXII and with the Weybridge PPD than with PPD-S.

The low level of hypersensitivity following BCG vaccination is indicated by

TABLE 5

COMPARISON OF VARIOUS TUBERCULINS ON BCG-VACCINATED PERSONS

DESIGNATION OF TUBERCULIN	POST VACCINAL INTERVAL	DOSE OF TUBERCULIN	NUMBER TESTED	POSITIVE		DEGREE OF REACTION				
				Number	Per Cent	1+	2+	3+	4+	Doubtful
		mg.								
OT 550	2–3 months	0.1	390	354	90.8	27	242	84	1	32
PPD-S		0.0001	390	253	64.9	52	179	22	0	80
OT 550	2–3 months	0.1	317	295	93.1	18	198	77	2	19
RT Lot XXII		10 TU*	317	297	93.7	18	191	85	3	17
OT 550	2–3 months	0.1	412	396	96.1	26	266	104	0	14
PPD-S Tablet "B"		0.0001	412	203	49.3	87	111	5	0	135
OT 550	2–3 months	0.1	283	234	82.7	19	185	30	0	45
PPD-S Tablet "C"		0.0001	283	69	24.4	36	31	2	0	89
OT 562	4–5 months	0.1	40	39	97.5	1	32	6	0	1
Weybridge PPD		0.0002	40	40	100.0	0	40	0	0	0
PPD-S	2–3 months	0.0001	79	54	68.4	7	42	5	0	20
RT Lot XXII		10 TU*	79	69	87.3	2	48	19	0	9
PPD-S	2–3 months	0.0001	63	27	42.9	5	19	3	0	28
PPD-S Tablet "B"		0.0001	63	13	20.6	4	7	2	0	26
PPD-S	4–5 months	0.0001	62	33	53.2	6	26	1	0	15
Weybridge PPD		0.0002	62	56	90.4	11	43	1	1	4
OT 550	1–4 years	0.01	201	57	28.4	9	41	7	0	100
PPD-S		0.00002	201	33	16.4	10	21	2	0	65
OT 550	1–4 years	0.01	131	42	32.1	5	34	3	0	62
PPD-S Tablet "B"		0.00002	131	15	11.5	5	10	0	0	32
OT 550	1–4 years	0.01	101	39	38.6	5	34	0	0	37
PPD-S Tablet "C"		0.00002	101	9	8.9	4	4	1	0	15
OT 550	1–4 years	0.1	101	77	76.2	12	59	6	0	22
PPD-S		0.0001	101	35	34.7	13	21	1	0	44
OT 550	1–4 years	0.1	98	79	80.6	9	61	9	0	17
PPD-S Tablet "B"		0.0001	98	17	17.3	9	8	0	0	34
OT 550	1–4 years	0.1	55	47	85.5	5	32	10	0	7
PPD-S Tablet "C"		0.0001	55	19	34.5	4	15	0	0	17
OT 550	6-36 months	0.1	76	68	89.5	4	50	14	0	8
RT Lot XXII		10 TU*	76	49	64.5	4	41	4	0	22
OT 550	6-36 months	0.1	214	164	76.6	3	125	33	3	46
Weybridge PPD		0.0002	214	113	52.8	7	94	12	0	94

* One TU equals 0.000013 mg. of purified tuberculin.

the fact that, of the definite reactions, only a small per cent followed the initial dose of 0.01 mg. of OT or 0.00002 mg. of PPD. In contradistinction, among those who appeared to have undergone a natural infection, a large per cent of the definite reactions occurred following the small dose of tuberculin. The greater potency of OT 550 as compared with PPD-S and PPD-S tablets was further indicated by the significantly higher per cent who reacted to 0.01 mg. of OT than to 0.00002 mg. of PPD-S or PPD-S tablets.

Significant as were the differences in the incidence of reactors to OT 550 and PPD-S among the recently vaccinated persons, the differences were even more

marked among those vaccinated from one to four years previously who were tested with OT 550 and the different purified tuberculins. It will be noted that 76.2 to 85.5 per cent reacted to 0.1 mg. of OT 550, while 17.3 to 34.7 per cent reacted either to PPD-S or PPD-S tablets. Among those tested six to thirty-six months after vaccination with 0.1 mg. of OT 550 and 10 T. U. of RT or PT XXII or Weybridge PPD, the degree of reaction was again more marked with the OT than with the other two preparations of purified tuberculin.

Differences in the potency of OT and purified tuberculin in BCG-vaccinated persons have also been observed by Dr. A. W. Dahlstrom of the Bureau of Indian Affairs, U. S. Department of the Interior (26). He found that, of 483 Indian children vaccinated with several different lots of BCG vaccine prepared by the Henry Phipps Institute, Philadelphia, Pennsylvania, who were tuberculin-tested approximately two months later with 0.0001 mg. of RT or PT XVIII and 0.1 mg. of OT 416, 41.8 and 81.8 per cent reacted to RT or PT and OT, respectively.

Comparison of Tuberculin-Patch and Intracutaneous Tests in BCG-Vaccinated Persons

There is a paucity of published data dealing with the comparative sensitivity of the tuberculin patch test and the intracutaneous test following BCG vaccination. To determine the relative sensitivity of the two procedures, 123 males, ranging in age from fifteen to twenty years, were tested by the simultaneous application of the patch test to the cleansed skin in the interscapular region and the intracutaneous injection of 0.1 mg. of OT 550 into the skin of the volar surface of the forearm. This group had received the same lot of BCG vaccine two months previously. Of the 123 persons tested, 118 (95.9 per cent) reacted to the intracutaneous test and 63 (51.2 per cent) reacted to the patch test, which was interpreted after both forty-eight and ninety-six hours.

In the experience of the present writers, the patch test, in adults, has not been as sensitive as the intracutaneous test. On the other hand, of a group of 2,401 infants vaccinated intracutaneously twenty-four to forty-eight hours after birth and tested with the patch test two months to two years after vaccination, 2,362 (98.4 per cent) gave a definite reaction to this test. It was observed that the level of tuberculin hypersensitivity in BCG-vaccinated persons, as indicated by the intensity of the reaction following either the patch test or the intracutaneous test, is significantly higher among infants than among BCG-vaccinated adults who have received the same preparation of BCG vaccine.

Specificity of the Tuberculin Reaction

The specificity of the tuberculin reaction has been generally accepted, and it has been assumed that the metabolic products of either acid-fast saprophytes or nonacid-fast bacilli are innocuous to tuberculous animals. The studies of B. and E. Lange (27), among others, showed that the metabolic products of some acid-fast saprophytes are capable of inducing a tuberculin reaction in man and in tuberculous animals. Cabasso (28) prepared a tuberculin from a nonpathogenic acid-fast organism isolated from a

fly. This tuberculin induced a reaction in tuberculous guinea pigs comparable to that induced by tuberculin from mammalian types of tubercle bacilli. Hauduroy (29) has compiled a list of various acid-fast saprophytes, many of which produce metabolic products which elicit a tuberculin reaction in man and in tuberculous animals.

Since the reaction to crude tuberculin preparations may in part be nonspecific, the advent of purified tuberculin prepared from cultures grown on synthetic medium eliminated some of the factors responsible for nonspecific reactions. McCarter, Getz, and Stiehm (30) compared samples of PPD prepared from avian tubercle bacilli and from *M. smegmatis* with PPD from human-type tubercle bacilli. Of 739 students tested with human and avian PPD, 22.3 per cent more reacted to the avian PPD than to the human PPD; while, of 464 students tested with human and smegmatis PPD, 14 per cent more reacted to the smegmatis PPD than to human PPD. Aronson, Saylor, and Parr (31) found that the incidence of reactions to purified tuberculin prepared by Henderson (32) from various acid-fast organisms varied in different parts of the United States. Thus, a larger per cent of Indians living in Arizona reacted to 0.00002 mg. of PPD prepared from *M. phlei*, *M. thamnopheos*, or *M. smegmatis* than did Indians living in South Dakota. These investigators also found that, among natives of Southeastern Alaska who had not been in contact with cattle or hogs and who used only powdered milk, of 103 children tested with 0.00002 mg. of purified protein from *Br. abortis*, 63 (61.1 per cent) reacted; while, of 38 children injected with 0.0002 mg. of the purified *Br. abortus* protein, 31 (81.6 per cent) reacted. The highest per cent of reactors and the most marked reactions occurred among those with a high level of tuberculin hypersensitivity.

Green (13) investigated the specificity of PPD prepared from human, bovine, and avian types of tubercle bacilli, from BCG, *M. phlei*, and Johne's bacillus. He found that guinea pigs sensitized with a specific organism showed a higher sensitivity to the specific PPD than to PPD prepared from the other acid-fast bacilli. Cross-reactions were observed when the dose of the nonspecific PPD was increased. Samples of PPD prepared from the human, bovine, or BCG strains of tubercle bacilli were comparable in their specificity.

While man and tuberculous animals may react to the metabolic products of acid-fast saprophytes and nonacid-fast bacilli, Crawford (33) has shown that animals infected with different acid-fast saprophytes react to Old Tuberculin prepared from mammalian or avian types of tubercle bacilli.

To evaluate further the specificity of PPD, the present writers have conducted comparative tests with OT and avian PPD, OT and balnei PPD on BCG-vaccinated persons, and OT and balnei PPD on a group of unvaccinated adults. Both preparations of PPD were kindly supplied by Mr. A. B. Paterson of Dr. H. H. Green's laboratory at Weybridge, England. The balnei PPD was prepared from an acid-fast organism isolated by Norden and Linell (34) from chronic ulcers of the skin of persons swimming in a pool in Sweden. This organism they have designated as *M. balnei*.

The results of the comparative tests on both BCG-vaccinated and unvaccinated persons are presented in table 6.

It will be noted from table 6 that the incidence of positive reactions to 0.1 mg. of OT 550 and to 0.0002 mg of Weybridge Avian PPD two to three months following BCG vaccination is approximately the same for both preparations. Of

TABLE 6

COMPARISON OF OLD TUBERCULIN WITH PURIFIED PROTEIN DERIVATIVE FROM M. AVIUM AND M. BALNEI

DESIGNATION OF TUBERCULIN	POST-VACCINAL INTERVAL	DOSE	NUMBER TESTED	POSITIVE		DEGREE OF REACTION				
				Number	Per Cent	1+	2+	3+	4+	Doubtful
		mg.								
OT 550	2–3 months	0.1	184	180	97.8	4	135	41	0	4
Weybridge Avian PPD		0.0002	184	176	95.7	11	147	18	0	9
OT 550	1–4 years	0.01	123	59	48.0	5	50	4	0	63
Weybridge Balnei PPD		0.00002	123	14	11.4	11	3	0	0	42
OT 550	2–3 months	0.1	48	46	95.8	0	32	13	1	2
Weybridge Balnei PPD		0.0001	48	34	70.8	1	28	5	0	13
OT 550	Unvaccinated population	0.01	105	99	94.3	2	55	40	2	6
Weybridge Balnei PPD		0.00002	105	81	77.1	24	51	6	0	11

those tested with 0.01 mg. of OT and 0.00002 mg. of the balnei PPD one to four years after vaccination, the incidence of reactions is smaller with balnei PPD and the degree of reaction is weaker than that following OT. Furthermore, a large number of doubtful or atypical reactions were observed with both OT and PPD. When the dose of OT 550 and balnei PPD was increased to 0.1 and 0.0001 mg., respectively, among those vaccinated two to three months previously, the per cent of those who reacted both to OT and balnei PPD rose sharply and the number of 2- and 3-plus reactions increased.

The balnei PPD and OT 550 were compared on a group of unvaccinated persons. It was found that, with 0.01 mg. of OT and 0.00002 of PPD, fewer persons reacted to the balnei PPD and the degree of reaction was weaker than with the OT.

SUMMARY

The relative sensitivity of different samples of Old Tuberculin (OT) and different preparations of purified tuberculins was compared by the simultaneous intracutaneous injection of paired tuberculins in unvaccinated and in BCG-vaccinated persons.

The potency of different samples of OT, as determined on both vaccinated and unvaccinated persons, was found to differ. The differences were most marked among those vaccinated with BCG vaccine one to four years previously.

The activity of OT was found to be decreased after freeze-drying.

Different preparations of purified tuberculins, except PPD-S tablets, showed no significant differences in potency when tested on highly sensitized persons.

Among unvaccinated persons with a high level of tuberculin hypersensitivity,

the incidence of positive reactions to the usual first dose of the different purified tuberculins was approximately the same.

Among BCG-vaccinated persons tested two to five months after vaccination with an intermediate dose of OT and dosages of PPD-S up to 0.0001 mg. in strength, a significantly higher per cent reacted to the Old Tuberculin than to the PPD-S, while with a Danish preparation of PPD labeled RT or PT XXII or with the English preparation labeled Weybridge PPD, the results were comparable to those with OT.

Differences in the incidence of reaction to OT 550 and the different preparations of purified tuberculins were most marked among those who had received BCG vaccine one to four years previously.

PPD-S tablets gave a significantly lower per cent of reactions, in both unvaccinated and BCG-vaccinated persons, than did PPD-S solution or OT 550.

Among BCG-vaccinated persons, a comparable per cent reacted to both PPD from *M. avium* and to OT 550, while a smaller per cent reacted to PPD from the acid-fast *M. balnei* organism.

Among the unvaccinated population, a somewhat smaller per cent reacted to PPD from *M. balnei* than to OT 550.

The patch test gave a significantly lower per cent of reactions in both the unvaccinated and BCG-vaccinated persons than did the intracutaneous injection of two different samples of OT or PPD-S.

SUMARIO

Comparación de Algunas Tuberculinas en Sujetos Vacunados y no Vacunados con BCG por medio de la simultánea inyección intracutánea de tuberculinas apareadas en personas vacunadas y no vacunadas con BCG, se comparó la relativa sensibilidad a distintas mezclas de Tuberculina Antigua (TA) y de diversas preparaciones de tuberculinas purificadas

Observóse que variaba la potencia de distintas muestras de TA, al ser determinada tanto en personas vacunadas como no vacunadas. Las diferencias fueron más notables entre las vacunadas con BCG de uno a cuatro años antes.

Observóse que la actividad de la TA disminuía después de la congelación-desecación.

Diversas preparaciones de tuberculinas purificadas, con excepción de las tabletas de PPD-S, no revelaron mayores diferencias en potencia al ser comprobadas en personas muy sensibilizadas.

Entre las personas no vacunadas con un alto tenor de hipersensibilidad a la tuberculina, fué aproximadamente idéntica la incidencia de reacciones positivas a la habitual primera dosis de las distintas tuberculinas purificadas.

Entre los sujetos vacunados con BCG, comprobados de dos a cinco meses después de la vacunación con una dosis intermedia de TA y dosis de PPD-S hasta de 0.0001 mg., un porcentaje significativamente más alto reaccionó a la TA que al PPD-S, mientras que con una preparación danesa de PPD rotulada RT o PT XXII o con la preparación inglesa rotulada "Weybridge PPD", los resultados fueron comparables a los obtenidos con TA.

Las diferencias en la incidencia de reacciones a TA 550 y a las distintas preparaciones de tuberculinas purificadas fueron más notables entre los que habían recibido vacuna BCG de uno a cuatro años antes.

Las tabletas de PPD-S produjeron un porcentaje significativamente más bajo de reacciones que la solución de PPD-S o que la TA 550 tanto entre los no vacunados como en los vacunados con BCG.

Entre los vacunados con BCG, un porcentaje comparable reaccionó tanto al PPD obte-

nido del *M. avium* como a la TA 550, en tanto que un por ciento menor reaccionó al PPD obtenido del microbio ácidorresistente *M. balnei*.

Entre la población no vacunada, un porcentaje algo menor reaccionó al PPD obtenido del *M. balnei* que a la TA 550.

La prueba del parche arrojó un porcentaje significativamente menor de reacciones que la inyección intracutánea de dos muestras distintas de TA o de PPD-S tanto en los no vacunados como en los vacunados con BCG.

RESUME

Etude comparative de quelques tuberculines chez des sujets vaccinés ou non vaccinés à la tuberculine

L'activité relative de différents échantillons de vieille tuberculine (OT) et de différentes préparations de tuberculines purifiées fut comparée par l'injection intradermique de tuberculines appariées chez des sujets vaccinés ou non par le BCG.

Une différence d'activité entre les différents spécimens de vieille tuberculine a été constatée chez les sujets vaccinés et chez les non vaccinés. Cette différence était la plus accentuée parmi ceux ayant été vaccinés par le BCG un à quatre ans auparavent.

L'activité de la vieille tuberculine a été trouvée réduite après dessiccation par congélation.

Les différentes préparations de tuberculines purifiées, sauf les comprimés PPD-S, ne présentaient pas de différence d'activité significative quand elles étaient testées chez des sujets très allergiques.

Parmi les sujets non vaccinés ayant un haut degré de sensibilité à la tuberculine, l'incidence des réactions positives à la dose initiale usuelle des diverses tuberculines purifiées était sensiblement la même.

Parmi les sujets vaccinés par le BCG qui furent testés deux ou cinq mois après vaccination avec une dose moyenne de tuberculine et des doses de PPD-S allant jusqu'à 0,0001 mg., le pourcentage de réactions obtenues avec la vieille tuberculine a été notablement plus élevé qu'avec la tuberculine PPD-S; toutefois, avec la préparation danoise de PPD-S dénommée RT ou PT XXII ou avec la préparation anglaise dénommée "Weybridge PPD" les résultats étaient comparables à ceux obtenus avec la vieille tuberculine.

Les écarts dans l'incidence de la réaction à OT 550 et aux différentes préparations de tuberculines purifiées étaient les plus marquées dans le groupe des sujets ayant reçu le vaccin BCG un à quatre ans auparavant.

Le taux des réactions avec les comprimés PPD-S était significativement plus bas qu'avec le PPD-S en solution ou avec OT 550 à la fois chez les sujets vaccinés par le BCG ou les non vaccinés.

Parmi les sujets vaccinés par le BCG, le taux des réactions à la tuberculine PPD de *M. avium* et à OT 550 était comparable, tandis que le pourcentage de ceux qui réagissaient au PPD dérivé du *M. balnei* acido-résistant était plus faible.

Parmi la population non vaccinée, le taux des réactions au PPD de *M. balnei* était un peu plus faible que celui des réactions à OT 550.

L'épidermo-réaction donnait un taux de réactions positives plus faible chez les sujets vaccinés par le BCG ou les non vaccinés que l'injection intradermique de deux échantillons différents de OT ou de PPD-S.

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QUANTITATIVE OBSERVATIONS ON THE PATTERN OF EMERGENCE OF RESISTANCE TO ISONIAZID[1, 2, 3]

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INTRODUCTION

It has been established that, in patients with tuberculosis who are treated with isoniazid and who continue to discharge tubercle bacilli, evidence may be obtained of the emergence of drug resistance in some of the bacilli isolated (1–6). All wild-type strains of tubercle bacilli, although predominately susceptible to isoniazid, contain relatively large numbers of drug-resistant mutants. During therapy a change in bacterial population in the patient is detectable as a shift toward a higher proportion of the more resistant bacterial cells. There is little doubt that when isoniazid is employed as the sole therapy this shift within the bacterial population occurs rapidly and is of considerable magnitude.

Nearly all of the observations of this process thus far reported have been carried out by one of two methods. These methods involve either direct culture of specimens or inoculation of a subculture into a series of tubes of solid culture medium containing graded concentrations of isoniazid. After appropriate incubation an estimate of the growth in each concentration of drug is made and compared with that of the control tube.

Whereas these methods are satisfactory for routine use, they are at best only semiquantitative. Variations in numbers of bacilli in specimens cultured directly make serial observations difficult, and when the numbers are low the readings often fail to reveal significant proportions of resistant cells. Moreover, comparison of the relative numbers in two tubes when the numbers of bacilli are high is unreliable. An additional source of error is the tendency for colonies on egg media to increase in size as the inoculum becomes smaller.

More careful quantitative observations on the emergence of resistance to isoniazid seemed to be important for two reasons conceivably quite divergent in their implications concerning the usefulness of the drug. On the one hand, the most obvious effect of the emergence of high degrees of drug resistance would be expected to be a loss of drug effect. On the other hand, there is considerable evidence that tubercle bacilli which are highly resistant to isoniazid have diminu-

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[3] The isoniazid used in this study was generously supplied by E. R. Squibb & Sons, Division of Mathieson Chemical Corporation, New York.

tion or even virtual loss of pathogenicity for guinea pigs, a property hitherto considered virtually synonymous with pathogenicity for humans (7–12). Were these highly resistant strains to prove of diminished virulence for humans, it would obviously be desirable to attempt to achieve in patients a state of high resistance.

Accordingly, it seemed of considerable interest to determine more accurately the quantitative aspects of the emergence of isoniazid resistance in an attempt to learn whether a high degree of resistance occurs with regularity in patients under treatment. The present report summarizes the quantitative data obtained in cultures from a small group of patients with pulmonary tuberculosis treated with isoniazid as the sole therapeutic agent.

MATERIALS AND METHODS

Specimens of sputum or gastric aspirate were treated with sodium hydroxide, neutralized and centrifuged for concentration. Portions of the concentrate were then inoculated onto Petragnani's medium and onto oleic-acid–albumin solid medium containing 25 units of penicillin per ml. Subculture from primary isolation thus accomplished was made into liquid Tween®-albumin medium and the strains were carried in this medium thereafter. Care was taken to obtain a large inoculum for the initial subculture. In instances in which growth on solid medium was not heavy, the entire growth was inoculated into the liquid medium to ensure a representative sample.

Enumeration of the bacilli resistant to various concentrations of isoniazid was made by a technique essentially the same as that described by Fenner, Martin, and Pierce (13). Appropriate dilutions of a seven-day growth in liquid medium were first made. Three measured replicate drops of 0.02 ml. each of each dilution were placed on the surface of solid oleic-acid–albumin medium containing the following concentrations of isoniazid in micrograms per milliliter: 0.1, 1.0, and 10.0. Similar inoculation was made onto a control plate containing no isoniazid. These were then incubated and colony counts were made at two and at three weeks. (Further incubation up to eight weeks was shown not to yield further growth.) From these counts calculation was made of the total bacterial population and of the proportion of cells in each culture resistant to each concentration of isoniazid.

In parallel with the above counts, drug-susceptibility tests were performed in liquid medium. These consisted simply of twofold serial dilution tests carried out in both Tween®-albumin and oleic-acid–albumin liquid media. End points were read as the lowest concentration of isoniazid which inhibited growth for two weeks.

The cultures studied were chosen from strains of tubercle bacilli isolated from sputum or gastric aspirate in a group of 47 patients. Those chosen included all patients in the group from whom strains had been isolated prior to treatment and on at least two occasions at intervals of a month or longer subsequent to initiation of therapy. These criteria would thus be expected to include those patients with the poorest response to therapy and with the maximum opportunity for development of bacillary resistance.

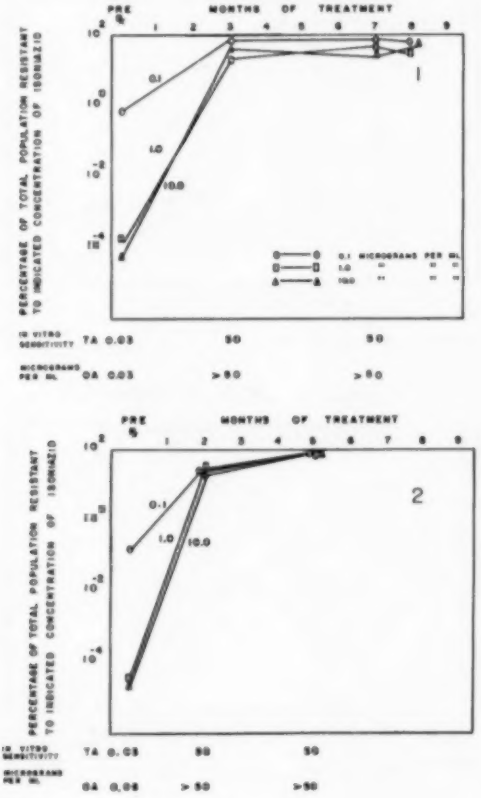
RESULTS

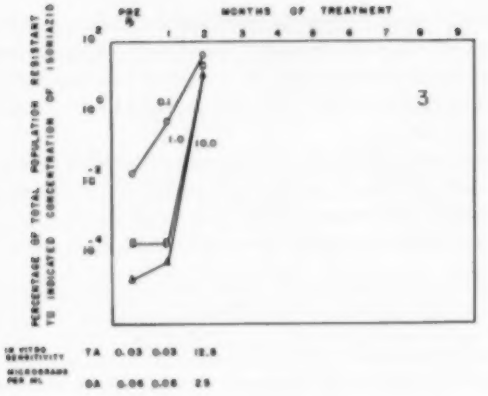
The observations are most conveniently presented in graphic form and are shown in figures 1 through 11. In each graph the ordinate indicates the percentage of the total population resistant to the specified concentration of isoniazid, three concentrations being plotted on each graph, 0.1, 1.0, and 10.0 γ per ml.

The abscissa in each graph represents the duration of therapy. Along the abscissa is also represented the *in vitro* susceptibility of each strain as measured in liquid medium. Parallel tests were carried out in Tween®-albumin (TA) and in oleic-acid–albumin (OA) liquid media. The results of both tests are indicated along the bottom of each graph.

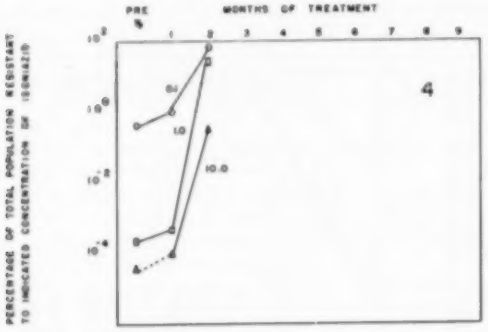
Examination of these graphs reveals several points of interest. In all patients studied the cultures obtained subsequent to initiation of therapy showed an increase in the number of resistant cells. In general, those cells resistant to 0.1 γ of isoniazid per ml. showed a rapid rise in numbers. With two exceptions (*Cases*

FIGS. 1 through 11. Each graph illustrates the isoniazid-resistant mutants in a series of cultures obtained from one patient prior to and during therapy with isoniazid. Each culture was examined for mutants resistant to 0.1, 1.0, and 10.0 γ of isoniazid per ml. and the results were plotted as the percentage of the total population of each strain resistant to each of these concentrations of isoniazid. Across the bottom of each chart is indicated the *in vitro* sensitivity to isoniazid of each strain as tested in two liquid media, Tween®-albumin (TA) and oleic-acid–albumin (OA).

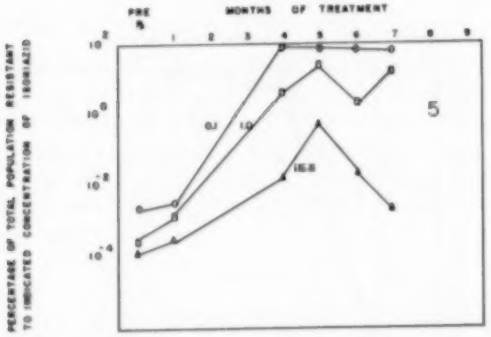




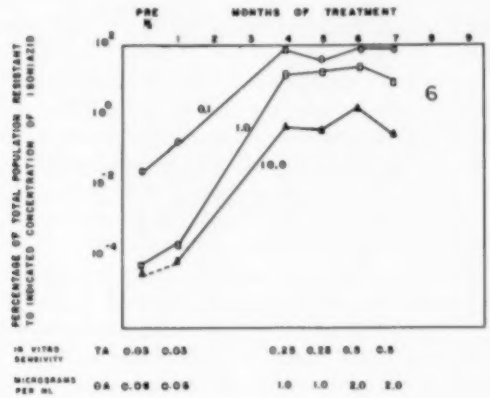
IN VITRO SENSITIVITY	TA	0.03	0.03	12.5	
MICROGRAMS PER ML	SA	0.06	0.06	25	

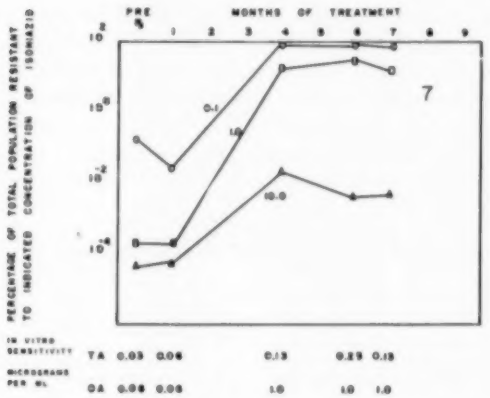


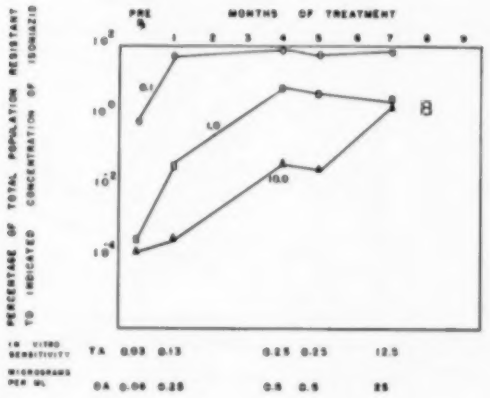
IN VITRO SENSITIVITY	TA	0.03	0.03	6.3
MICROGRAMS PER ML	SA	0.03	0.03	12.5

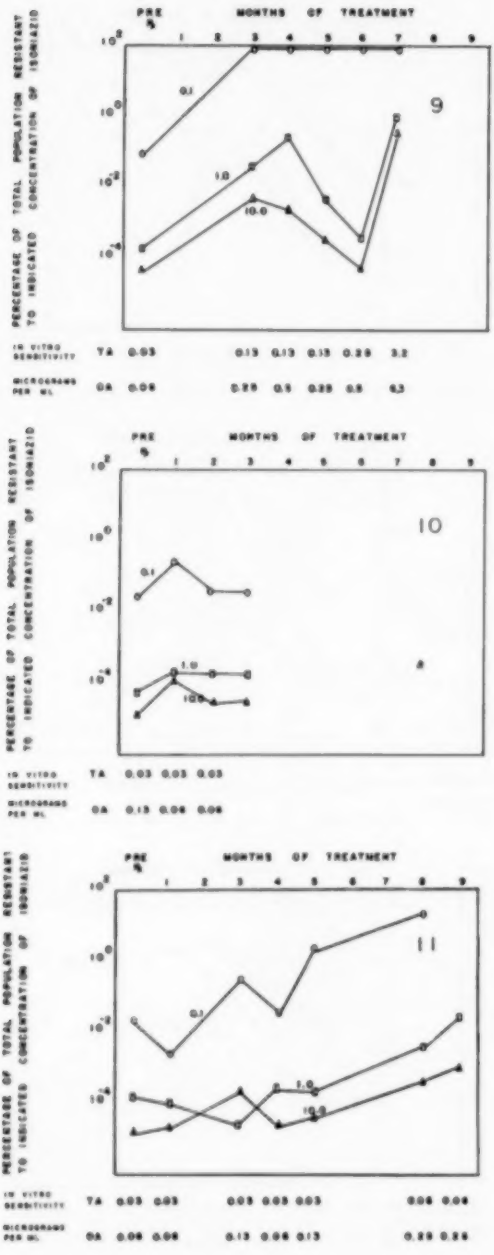


IN VITRO SENSITIVITY	TA	0.03	0.03	0.25	0.5	0.5	0.5
MICROGRAMS PER ML	SA	0.06	0.06	0.5	1.0	1.0	2.0


PRE
%
MONTHS OF TREATMENT
0 1 2 3 4 5 6 7 8 9
10^2
10^0
10^{-2}
10^{-4}
0.1
1.0
10.0
6
PERCENTAGE OF TOTAL POPULATION RESISTANT TO INDICATED CONCENTRATION OF ISONIAZID
IN VITRO SENSITIVITY
TA 0.03 0.03 0.25 0.25 0.5 0.5
MICROGRAMS PER ML
0A 0.06 0.06 1.0 1.0 2.0 2.0


PRE
%
MONTHS OF TREATMENT
0 1 2 3 4 5 6 7 8 9
10^2
10^0
10^{-2}
10^{-4}
0.1
1.0
10.0
7
PERCENTAGE OF TOTAL POPULATION RESISTANT TO INDICATED CONCENTRATION OF ISONIAZID
IN VITRO SENSITIVITY
TA 0.03 0.06 0.13 0.25 0.13
MICROGRAMS PER ML
0A 0.06 0.06 1.0 1.0 1.0


PRE
%
MONTHS OF TREATMENT
0 1 2 3 4 5 6 7 8 9
10^2
10^0
10^{-2}
10^{-4}
0.1
1.0
10.0
8
PERCENTAGE OF TOTAL POPULATION RESISTANT TO INDICATED CONCENTRATION OF ISONIAZID
IN VITRO SENSITIVITY
TA 0.03 0.13 0.25 0.25 12.5
MICROGRAMS PER ML
0A 0.06 0.25 0.5 0.5 25


PRE
MONTHS OF TREATMENT
PERCENTAGE OF TOTAL POPULATION RESISTANT TO INDICATED CONCENTRATION OF ISONIAZID
0.1
1.0
10.0
9
10
11
IN VITRO SENSITIVITY
MICROGRAMS PER ML

10 and *11*) most of the cells were soon resistant to this low concentration of drug.

In some instances (*Cases 1* and *2*) mutants resistant to 1.0 γ of isoniazid per ml. also reached a high level, 30 per cent or more, within two or three months of therapy and continued to increase thereafter. In other instances (*Cases 5–9*) they showed a similar increase but then appeared to level off in the range of 10 to 30 per cent or less of the total population.

In 7 of the 11 cases it was never possible to demonstrate that more than 30 per cent of the cells present were resistant to 1 γ of isoniazid per ml., and generally a much lower percentage of these variants was found.

In 3 instances (*Cases 1–3*) mutants resistant to 10 γ of isoniazid per ml. were found to be present consistently in large numbers, i.e., they made up more than 10 per cent of the total population. In only 2 other individual cultures (*Cases 6* and *8*) did these mutants reach levels of more than 1 per cent of the total population.

Comparison of the figures at the bottom of each chart indicates that the *in vitro* susceptibility as determined in liquid medium gives a reasonably good indication of the change in bacterial population. Indeed, it appears to provide a value which may be useful clinically and is a practicable procedure, whereas the precise enumeration used in the present study is not practicable on a large scale.

As may be seen, drug-susceptibility testing in Tween®-albumin medium frequently gave slightly lower values for the minimal inhibitory concentration

TABLE 1

SUSCEPTIBILITY OF TUBERCLE BACILLI TO ISONIAZID AS TESTED IN LIQUID MEDIUM

MONTHS OF TREATMENT	MINIMAL INHIBITORY CONCENTRATION IN MICROGRAMS PER MILLILITER		
	<0.1	0.1–1.0	>1.0
Pretreatment	37	0	0
1	19	2	0
2	4	5	3
3	2	6	4
4	1	8	3
5	1	7	2
6	2	5	0
7	0	4	4
8	0	3	4
9	0	2	2
10	0	4	2
11	0	5	3
12	0	7	4
13	0	5	3
14	0	3	3
15	0	2	2
16	0	1	1
17	0	1	1
18	0	1	1
19	0	1	1
20	0	1	0

than in oleic-acid–albumin medium. This same effect has been noted previously with a variety of antituberculous drugs and is presumably the effect of the presence of Tween®. Its magnitude does not seem sufficiently great to alter the usefulness of the test, whichever medium is chosen, so long as the same medium is used consistently.

The data in table 1 are the results to date of the drug-susceptibility tests in liquid medium of the strains from all patients thus far observed on treatment with isoniazid alone. The same trend toward early development of resistance and the frequency of intermediate degrees of resistance described above are again reflected in these data.

DISCUSSION

These observations bring out clearly the complexity of the process of the emergence of isoniazid-resistant mutants under therapy and add further weight to the statement made by McDermott and associates (14) in an early phase of the work with isoniazid that "the question of isoniazid resistance is much more complicated than is the case with streptomycin."

The data obtained are in general agreement with observations reported many previous times to the effect that, when tubercle bacilli can be recovered from patients subsequent to the initiation of isoniazid therapy, an obvious change in bacterial population with respect to inhibition by this drug soon becomes evident. In the present study, when careful quantitative studies were made on the proportion of each culture susceptible or resistant to isoniazid, however, it was readily apparent that marked variations in the speed and magnitude of the development of resistance were seen in this small group of patients. The degree of this change with respect to the lowest concentration of isoniazid (0.1 γ per ml.) was particularly marked. In many instances (9 of the 11), however, the preponderance of cells in the culture continued to be inhibited by 1.0 γ of isoniazid per ml., a concentration which is readily attained *in vivo*. This was especially striking in *Cases 5* through *9* and *Case 11*. These patients were observed during seven to nine months of therapy, and at all times at least 70 per cent and generally more of the organisms obtained in their cultures were inhibited by 1.0 γ of isoniazid per ml.

It is apparent, therefore, that the uniformity of the population in a "resistant" strain must always be suspect unless steps have been taken to ensure that such uniformity is indeed the case. As previously mentioned, the uniform development of a high degree of resistance could have at least two divergent implications, loss of drug effect or the diminished pathogenicity which has been demonstrated in guinea pigs. The heterogeneity of the bacterial populations in the cultures of the present study would indicate that great caution should be exercised in interpretation of any culture as "resistant," whichever implication is being considered.

The observations reported add weight to the evidence that the apparently conflicting results reported on pathogenicity of "resistant" cultures for guinea

pigs could be explained by the presence of many fully virulent but drug-susceptible cells in the so-called resistant cultures.

From the data reported it does not seem possible to draw any conclusion with reference to the time at which neutralization of drug effect may be anticipated. In unpublished experiments, however, it has been demonstrated that an increase in intermediate or highly resistant mutants to as little as 1 to 4 per cent of the total population is highly significant in terms of reduction of drug effectiveness in mice infected with such strains.

Certain objections may be raised to the technique utilized in the *in vitro* tests used in the present study. Such tests involving subcultures may be in error if the mutants of varying degrees of resistance have different growth rates. Repeated observations on the same cultures, including strains of widely differing isoniazid susceptibility, have given quite consistent results, and, hence, it is believed that this objection is minimized. A more serious objection stems from the possibility that the medium employed lacks certain metabolites required by the resistant cells but not by the drug-susceptible ones. Lacking further definition of these nutritional requirements, this objection was not circumvented in these studies.

SUMMARY

Data have been presented on the *in vitro* susceptibility to isoniazid of tubercle bacilli from a group of patients treated with this drug as the sole antimicrobial agent. These data confirm the observations previously made by others that, when tubercle bacilli are still recoverable from patients under isoniazid therapy, a rapid change occurs in the makeup of the bacterial population with respect to inhibition by isoniazid. Quantitative observations on the cultures in the present study, however, strikingly reveal the complexity of this process and emphasize the need for extreme caution in drawing conclusions concerning the precise time required for neutralization of drug effect. Although high degrees of bacterial resistance may occur early in the course of therapy, this is by no means an invariable occurrence.

Further observations should be made on this phenomenon utilizing, if possible, techniques which would permit enumeration of mutants of various degrees of resistance in direct cultures of infected materials.

SUMARIO

Observaciones Cuantitativas acerca de la Formación de Resistencia a la Isoniacida

Los datos presentados versan sobre la susceptibilidad *in vitro* a la isoniacida de bacilos tuberculosos procedentes de un grupo de enfermos tratados con dicha droga como único agente antimicrobiano. Confirman esos datos anteriores observaciones ajenas de que, cuando hay todavía bacilos tuberculosos obtenibles en enfermos sometidos a la isoniacidoterapia, tiene lugar una rápida modificación en la composición de la población bacteriana con respecto a inhibición por la isoniacida. No obstante, las observaciones cuantitativas realizadas en los cultivos en el estudio actual revelan elocuentemente la complejidad de ese proceso y recalcan la necesidad de desplegar suma cautela al sacar conclusiones acerca del tiempo preciso requerido para la neutralización del efecto medicamentoso. Aunque pueden pre-

sentarse tenores elevados de resistencia bacteriana al principio de la terapéutica, esto no es en modo alguno constante.

Deben llevarse a cabo observaciones ulteriores sobre este fenómeno, utilizando, si es posible, técnicas que permitan la enumeración de las mutantes dotadas de distintos grados de resistencia en cultivos directos de las substancias infectadas.

RESUME

Observations quantitatives sur les modalités d'apparition de la résistance à l'Isoniazide

Présentation de données sur la sensibilité à l'isoniazide, *in vitro*, de bacilles de Koch provenant d'un groupe de malades recevant ce médicament comme unique agent antibactérien. Ces données confirment l'observation précédemment faite par d'autres auteurs que, en présence de bacilles tuberculeux récupérables chez des sujets soumis à l'isoniazidethérapie, il se produit un changement rapide dans la composition de la population bactérienne en relation avec l'inhibition par l'isoniazide. Dans l'étude actuelle, les observations quantitatives sur les cultures révèlent de façon saisissante la complexité de ce processus et mettent la nécessitée d'exercer une extrême prudence pour tirer des conclusions à l'égard du temps exact réclamé pour la neutralisation de l'action de l'isoniazide. Bien qu'un important degré de résistance bactérienne puisse se produire dès le début du traitement, cette manifestation est loin de se produire toujours.

Il y a lieu de poursuivre les observations sur ce phénomène, en utilisant, si possible, les techniques qui permettraient l'énumération des mutants de divers degrés de résistance dans les cultures directes de matières infectées.

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ISONIAZID THERAPY OF TUBERCULOUS PATIENTS AS A PREPARATION FOR PULMONARY RESECTION[1]

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INTRODUCTION

The present communication represents an attempt to evaluate the effectiveness of isoniazid in the preoperative preparation of patients for pulmonary resection. The possible theoretical objections to the use of a newly introduced drug as the sole treatment led to the selection, early in the study, of only those patients in whom streptomycin-resistant organisms had been found or suspected because of the clinical course of the disease. After the effectiveness of isoniazid and the lack of significant toxicity were apparent, this drug was used as the sole therapy for patients in whom resection was deemed advisable and who had received no streptomycin or para-aminosalicylic acid (PAS). The only criterion for selection was the expected availability for surgery shortly after the initiation of treatment.

The report is based on 71 patients who received isoniazid or iproniazid[2] as the sole antituberculous drugs in their preoperative period. The timing of surgical intervention was varied deliberately but was influenced somewhat by continued improvement, cavity closure, and similar considerations, particularly in the later period, so that some of the patients with the longest period of treatment were those in whom continued improvement was apparent. Early in the study, the regression of a tuberculous endobronchitis was all that was awaited before pneumonectomy or lobectomy.

PLAN OF INVESTIGATION

Fifty-eight patients received isoniazid, 50 mg. three times daily; 5 received 100 mg. three times daily; and 2 received 150 mg. three times daily. Iproniazid was used in dosages of 50 mg. four times daily for 6 patients and, unless otherwise specified, will be considered in the subsequent discussion without distinction from isoniazid.

The duration of preoperative treatment varied from two to thirty-two weeks (average 11 weeks). The drug was given up to and including the morning of operation, and was usually resumed as soon after surgery as oral medication was tolerated, which was usually the first postoperative day.

Close attention was given to possible toxic reactions. Careful hematologic and liver function studies, including bromsulfalein retention, Hanger's test, van den Bergh test, and prothrombin times, revealed no evidence of toxicity. Renal toxicity was not evident in weekly urinalyses and determinations of blood non-protein nitrogen.

All patients had some form of pulmonary resection: one had wedge resection; 31, segmental; 13, lobectomy; 13, lobectomy plus additional segmental or wedge resection; and 13, pneumonectomy. The pre-anesthetic medication consisted of scopolamine. Anesthesia

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[2] The isoniazid and iproniazid (Rimifon® and Marsilid®) used in this study were supplied by Hoffmann-LaRoche, Inc.

was usually induced with intravenous sodium amytal and maintained with ether, cyclopropane, nitrous oxide, or a combination of these agents. The most commonly used postoperative medication was Dilaudid,® although morphine and Dromoran® were also used.

METHODS AND MATERIALS

The surgical specimens were handled with sterile precautions. Within two to four hours after operation, representative areas of nodular and (if present) cavitary disease were removed. These portions of tissue were then pooled, minced, and ground in a mortar and pestle with the addition of a small amount of isotonic saline. After filtration through a loose cotton plug, the material was digested with a 3 per cent sodium hydroxide solution for forty-five minutes. Neutralization of the suspension was done with 25 per cent acetic acid. After centrifuging for twenty minutes, smears of the concentrates were stained and examined for acid-fast bacilli. Cultures from the concentrates were planted either on Jensen's modification of Löwenstein's medium or on American Trudeau Society medium. The cultures were incubated for eight weeks before being reported as negative. Six concentrates were also injected into guinea pigs. The animals were not sacrificed until at least eight weeks after inoculation. Isoniazid-susceptibility tests were made on all positive cultures. Due to a defective incubator, cultures were completed on only 49 of the 71 specimens.

After specimens for the bacteriologic study had been removed, the remaining lung tissue was inflated with air and preserved by injection of the bronchial tree with fixative and immersion in the fixative for one week. Serial slices at 0.5 to 1 cm. were made and blocks of tissue from representative disease areas were removed for microscopic examination. All microscopic sections were stained with hematoxylin and eosin.

The entire group of 71 surgical specimens was examined for gross and microscopic characteristics. The pathologic findings were classified under two major headings: *parenchymal disease* and *bronchial disease*, and compared with specimens from streptomycin- and PAS-treated groups.

In classifying in terms of parenchymal disease, the presence or absence of gross cavitation was noted. In the absence of cavitary disease, a search for liquefying nodules with central basophilia, cellular debris, and polymorphonuclear leukocyte infiltration was made. The dominant types of solid nodular disease were subdivided into three categories: *fibrocaseous nodules, cellular tubercules*, and a combination of the two nodular types.

The fibrocaseous nodules were defined as lesions with central caseation and a relatively dense acellular wall. In contrast, cellular tubercles were defined as lesions which were composed of epithelioid and giant cells with relatively little fibrous tissue or caseation.

The bronchial changes were placed in 5 groups: *bronchi normal, chronic bronchitis, tuberculous bronchitis, bronchiectasis without endobronchial tubercles*, and *bronchiectasis with endobronchial tubercles*. No attempt was made to determine the extent or severity of these changes. A diagnosis of bronchiectasis was made only if readily discernible gross dilatation and distortion of bronchi were noted. If tubercles, caseation, or tuberculous granulation tissue were found in the dilated bronchial wall, the specimen was classified as bronchiectasis with endobronchial tuberculosis. If bronchi of normal caliber contained tuberculous foci within the wall, a diagnosis of tuberculous bronchitis was made. The diagnoses of tuberculous bronchitis and bronchiectasis with endobronchial tuberculosis were not made if the only lesion was found at the bronchocavitary junction. Chronic bronchitis was the term used when a significant increase in lymphocytic and plasma cell infiltration of the bronchial wall occurred without evidence of the specific changes regarded as tuberculous.

OBSERVATIONS

Although assessment of results is based on the bacteriologic and pathologic findings, an additional attempt was made to tabulate the usual evidence of clin-

TABLE 1

THE RESULTS OF SPUTUM CULTURES OF 71 PATIENTS AT THE INSTITUTION OF ISONIAZID OR IPRONIAZID THERAPY AND IN THE IMMEDIATE PRE-SURGICAL PERIOD

	MICROSCOPY			CULTURE		
	Positive	Negative	Not Recorded	Positive	Negative	Not Recorded
Initial sputum	42	17	12	53	12	6
Preoperative sputum	14	56	1	15	53	3

TABLE 2

THE CLINICAL CLASSIFICATION OF 49 PATIENTS WHO RECEIVED ISONIAZID OR IPRONIAZID AS THE SOLE PREOPERATIVE CHEMOTHERAPEUTIC AGENT AND THE RESULTS OF SMEARS AND CULTURES OF THE RESECTED SPECIMENS

CLINICAL CLASSIFICATION OF PULMONARY TUBERCULOUS LESIONS	NUMBER OF CASES	MICROSCOPY FOR ACID-FAST BACILLI		CULTURES FOR M. TUBERCULOSIS	
		Positive	Negative	Positive	Negative
Minimal	4	3	1	0	4
Moderately advanced	18	15	3	4	14
Far advanced	27	20	7	7	20
Totals	49	38	11	11	38

ical improvement, such as roentgenographic clearing and status of infectiousness, prior to surgical intervention. The group as a whole included many patients in whom the chronic fibrocavernous type of disease precluded any marked roentgenographic change in a short course of therapy. In 50 patients, the disease showed little or no significant change, in 12 it was slightly improved, and in only 10 was there moderate or marked improvement in the chest roentgenogram. The control of fever, lessening of sputum volume, gain of weight, and feeling of well-being were noted in the majority of patients.

As a result of difficulties with a faulty incubator, several cultures were lost and, in several patients, the immediate pretreatment cultures were not obtained or were negative for tubercle bacilli. These results are summarized in table 1, and it may be seen that "sputum conversion" was common in the preoperative period.

Smears were made of 70 of the 71 resected specimens and, of these, 56 (80 per cent) were positive and 14 (20 per cent) were negative for acid-fast bacilli. The 49 tissue specimens for which cultures are available showed the same incidence of positive and negative smears, but only 11 (22 per cent) of the 49 specimens were positive for *M. tuberculosis* on culture. The data on the smears and cultures of the resected specimens are correlated with the extent of the patient's disease in table 2.

Drug-susceptibility tests were made on 10 of the 11 positive cultures. Seven of these strains of tubercle bacilli were completely susceptible to 5 γ of isoniazid per ml. One strain was resistant to 5 γ per ml., but was completely susceptible to 10 γ per ml. This strain was obtained from a gross cavity removed from a patient

TABLE 3

A Comparison of the Duration of the Preoperative Isoniazid or Iproniazid Therapy with the Smears and Cultures of the Resected Specimens

WEEKS OF THERAPY	NUMBER OF SPECIMENS	MICROSCOPY FOR ACID-FAST BACILLI		CULTURES FOR M. TUBERCULOSIS	
		Positive	Negative	Positive	Negative
2–8	21	17	4	7	14
9–16	15	14	1	4	11
17–24	10	6	4	0	10
25 or more	3	1	2	0	3

TABLE 4

A Comparison of the Cultures of Resected Specimens with the Duration of Streptomycin-PAS Therapy Prior to Starting Isoniazid and Iproniazid

MONTHS OF STREPTOMYCIN-PAS THERAPY PRIOR TO STARTING ISONIAZID OR IPRONIAZID	NUMBER OF SPECIMENS	POSITIVE	NEGATIVE
None	11	0	11
1–6 months	18	5	13
7–12 months	10	3	7
13 or more months	10	3	7

who had been treated for seven weeks. In 2 patients, in both of whom cavitary disease persisted, who had received ten to thirteen weeks of treatment preoperatively, the strains of *M. tuberculosis* cultured from the resected specimens were resistant to 50 and 100 γ of isoniazid per ml., respectively. Of the 7 strains susceptible to 5 γ of isoniazid per ml., 4 strains were from noncavitary disease of patients who had received eight to fourteen weeks of isoniazid therapy and 3 were from cavitary specimens from patients who had received four to seven weeks' preoperative therapy.

In table 3 the results of the cultures of the resected specimens and the duration of preoperative therapy are tabulated. The most significant observation is that no tubercle bacilli were cultured from the 13 resected specimens of patients who had received seventeen or more weeks of treatment. This may have been influenced somewhat by the timing of surgery, as it did tend to be delayed in the event of continued improvement. The findings in the patients who received previous PAS and streptomycin therapy were essentially similar, as shown in table 4. It is interesting to note, however, that tubercle bacilli could not be cultured from the 11 specimens removed from patients who had received only isoniazid.

As stated before, the selection of the patients was such that the persons who were selected for treatment with isoniazid alone had, as a rule, less extensive disease which, for that reason, was regarded as suited for excisional surgery after a relatively short term of chemotherapy. In patients from whom streptomycin-resistant strains of *M. tuberculosis* had been isolated, there was an understand-

able tendency to proceed with surgery without awaiting further improvement of endobronchitis or marked reduction of cavity size on the isoniazid therapy for fear of being unable to control such a problem should resistance to isoniazid develop.

The presence of residual cavity exerted an influence on the incidence of culturable tubercle bacilli. Gross cavitation was present in 19 of the 49 specimens on which the results of cultures were available. Of the 19 cavities, 15 showed acid-fast bacilli on microscopy and 7 were positive for *M. tuberculosis* on culture. Of these 7 cultures, 2 contained organisms highly resistant to isoniazid and one resistant to 5 γ but inhibited by 10 γ per ml. Twenty-three of the 30 noncavitary specimens were positive for acid-fast bacilli on smear but only 4 yielded cultures positive for tubercle bacilli. All of these 4 cultures were drug susceptible *in vitro*.

In table 5 the various types of parenchymal lesions in the isoniazid-treated group are compared with 136 specimens from patients who had received from one to four months of streptomycin-PAS preoperatively. The only notable difference was in the incidence of gross cavities, which was higher in the isoniazid group. It is believed that this is merely a reflection of the relatively large numbers of streptomycin-resistant cases among the patients selected. It may be seen in table 6 that there was relatively little difference between the two groups with respect to bronchial abnormalities.

The patients have been followed for nine to seventeen months postoperatively. Isoniazid alone was continued in the postoperative period for varied periods which averaged approximately six months unless extensive residual disease remained. Two patients have died, and 4 patients have continued to excrete tubercle bacilli throughout the period of observation. A 40-year-old white male died four weeks after a left pneumonectomy and one week after a secondary thoracoplasty. Necropsy revealed a ruptured aorta secondary to a tuberculous aortitis. The second death was due to chronic cor pulmonale in a 47-year-old white male five months after a right pneumonectomy. One patient developed a bronchopleural fistula. In this patient, no tubercle bacilli were demonstrated after the resection

TABLE 5

A Comparison of the Types of Parenchymal Lung Lesions in 71 Specimens Removed from Patients Who Received Isoniazid or Iproniazid with 136 Specimens Removed from Patients Who Received One to Four Months of Streptomycin-PAS

Parenchymal Lesion	Isoniazid or Iproniazid		Streptomycin-PAS	
	Number	Per Cent	Number	Per Cent
Fibrocaseous nodules	20	27	38	28
Cellular tubercles	11	16	31	23
Both fibrocaseous nodules and cellular tubercles	40	56	67	49
Gross cavities	24	34	31	23
Liquefying nodules	16	23	29	21
Noncavitary and nonliquefying lesions	31	43	76	56

TABLE 6

A COMPARISON OF THE TYPES OF BRONCHIAL DISEASE IN 70 SPECIMENS REMOVED FROM PATIENTS WHO HAD RECEIVED ISONIAZID OR IPRONIAZID (6 CASES) WITH 118 SPECIMENS REMOVED FROM PATIENTS WHO HAD RECEIVED ONE THROUGH THREE MONTHS OF STREPTOMYCIN-PAS THERAPY

BRONCHIAL FINDINGS	ISONIAZID OR IPRONIAZID		STREPTOMYCIN-PAS	
	Number	Per Cent	Number	Per Cent
Bronchi normal	2	3	12	10
Chronic bronchitis	24	34	32	27
Tuberculous bronchitis	16	23	27	23
Bronchiectasis without endobronchial tuberculosis	8	11	17	14
Bronchiectasis with endobronchial tuberculosis	19	27	30	25
Both types of bronchiectasis	27	38	47	39
Total specimens with endobronchial tuberculosis	35	50	57	48

and a secondary closure was successful. He remains well and has been discharged from the sanatorium.

Four patients either failed to "convert their sputum" after surgery or had recurrence of sputum containing tubercle bacilli. Some comment concerning these 4 patients is appropriate.

The first patient was a 45-year-old male who had extensive bilateral miliary type of disease with bilateral thin-walled cavities, first recognized in 1946. Renal tuberculosis was also present. Streptomycin-PAS had been used irregularly on several occasions and then continuously. A thin-walled cavity in the superior segment of the left lower lobe disappeared and then recurred on several occasions. Streptomycin-resistant tubercle bacilli had been isolated. After ten weeks of preoperative therapy with isoniazid, the cavity appeared to be filled in. The cavity-bearing segment was removed with considerable difficulty because of the marked pleural reaction and extensive nodular disease. This cavity was negative for tubercle bacilli on culture. The expansion of the lung was poor and a bronchopleural fistula persists. The patient continues to discharge tubercle bacilli but is in good clinical condition.

A diabetic male of 24 years had bilateral cavities. With streptomycin-PAS he gradually improved but, after almost two years of continuous treatment, the right-sided cavities reopened and he demonstrated clinical worsening. Isoniazid was given for nine weeks before a residual 2 cm. nodule, the site of a previous cavity, was removed from the left lung. Following surgery there was an increase in the roentgenographic shadows in the right lower lobe area and the sputum remained positive for acid-fast bacilli on microscopy. Isoniazid was continued alone for two months and the roentgenographic appearance of the chest had almost returned to the preoperative level. By this time the laboratory report of isoniazid resistance of 50 γ per ml. was received and streptomycin-PAS was added. Four months later there was no marked improvement in the chest roentgenogram, and his sputum remained positive for tubercle bacilli. At this time, December, 1952, the right upper lobe and superior segment of the right lower lobe were removed. There were some small "granular" areas of disease in the lateral and anterior basal segments, but it was not believed possible to remove these areas without doing a pneumonectomy. The upper lobe and the superior segment both contained cavities. Following surgery, the patient has stopped excreting tubercle bacilli and he has recently been discharged from the sanatorium. Cultures of the resected specimen revealed tubercle bacilli which were resistant to 100 γ of isoniazid and 10 γ of streptomycin per ml. of medium. This patient's

case is not included in the series because of the use of streptomycin-PAS in the preoperative preparation for the right lung surgery.

The third patient, a 26-year-old male, had moderately advanced tuberculosis. After ten weeks of isoniazid treatment the right upper lobe and superior segment of the right lower lobe were removed. Four weeks after surgery, a bronchopleural fistula with a small infected pneumothorax pocket appeared in the position of the segmental resection. The sputum was positive for tubercle bacilli by microscopy and culture. The therapy was changed to streptomycin-PAS. The roentgenographic changes gradually cleared and cultures of sputum and gastric washings have been negative for *M. tuberculosis*.

The fourth patient who continued to discharge tubercle bacilli following surgery was a 40-year-old man who had multiple pulmonary segments removed after fourteen weeks of isoniazid treatment. For ten months he was noninfectious and then tubercle bacilli reappeared in the sputum. No demonstrable roentgenographic change occurred during this period and the actual source of the tubercle bacilli was never determined. The patient's treatment was changed to streptomycin-PAS, and six months later his sputum was once again negative for tubercle bacilli on microscopy and culture.

COMMENT

The operations were accomplished in all of the patients without complications. No prolonged or excessive bleeding was noted. No incompatibilities between the isoniazid and iproniazid and the anesthetic agents or pre- or postoperative medications were noted, and no difficulties were encountered with a wide variety of drugs used throughout the treatment period. The surgical morbidity and mortality were low in spite of a high proportion of "poor risk" patients. The postoperative course of the patients to the present time has been comparable to that of patients treated with streptomycin-PAS.

SUMMARY

Tubercle bacilli could be cultured from only 11 of 49 tuberculous lesions removed from patients whose sole preoperative chemotherapy was isoniazid or iproniazid. Isoniazid and iproniazid (6 patients) were potent antituberculous agents in this group of patients, as judged by clinical, roentgenographic, and bacteriologic criteria.

SUMARIO

La Isoniacidoterapia de los Tuberculosos como Preparación para la Resección Pulmonar

No pudieron cultivarse bacilos tuberculosos más que de 11 de 49 lesiones tuberculosas extirpadas a enfermos cuya única quimioterapia preoperatoria consistió en isoniacida o iproniacida. La isoniacida y la iproniacida (6 enfermos) fueron potentes agentes antituberculosos en este grupo de pacientes, juzgadas por pautas clínicas, radiográficas y bacteriológicas.

RESUME

Isoniazide-thérapie du tuberculeux dans la préparation à la résection pulmonaire

Des cultures de bacilles tuberculeux n'ont été obtenues que dans onze cas sur 49 lésions tuberculeuses prélevées chez des sujets dont la seule chimiothérapie préopératoire consistait en isoniazide et iproniazide. Selon les critères cliniques radiologiques et bactériologiques, l'isoniazide et l'ipronizide se sont montrées des agents antituberculeux puissants dans ce groupe de patients (six malades).

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COEXISTING PULMONARY COCCIDIOIDOMYCOSIS AND TUBERCULOSIS[1]

A Review of Twenty-Four Cases

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INTRODUCTION

With the recent awareness of the incidence of coccidioidal infection, the recognition and treatment of coexisting pulmonary coccidioidomycosis and tuberculosis have assumed new importance. A review of the literature reveals 19 case reports (18 males and one female) of coexisting pulmonary coccidioidomycosis and tuberculosis. In the present paper, a series of 24 cases is reported, and an attempt is made to postulate the pathogenesis and outline the diagnosis and treatment of this combination of diseases.

OBSERVATIONS

Present Series

To facilitate analysis, pertinent features of the 24 cases are presented in tables 1 and 2*A* and 2*B*. The 19 cases described in the literature are summarized in table 3.

Surgically treated patients: There were 9 surgically treated patients. They ranged in age from thirty-one to sixty-two years; all of the patients were white; 5 were female and 4 were male. Coccidioidomycosis was diagnosed by sputum examination in 5 patients, by complement fixation in 3, and by examination of surgical specimens in 4 patients. The sputum was positive for acid-fast bacilli in all patients except one, in whom there was clinical and roentgenographic evidence of tuberculosis prior to the coccidioidal infection. All of the 9 patients have recovered completely and are now working full time.

Non-surgical patients: The non-surgical patients were divided into two groups, consisting of 8 infants and children and 7 adults. In the first group, the ages ranged from seven months to thirteen years. Coccidioidomycosis was diagnosed by complement fixation in all but one patient, in whom the diagnosis was made by sputum examination and culture. Tuberculosis was confirmed by culturing tubercle bacilli from sputum or gastric washings. All of these patients are still under observation, and 4 are in tuberculosis hospitals.

In the adult group, the ages ranged from twenty-two to fifty years; 3 of the patients were females and 4 were males. Coccidioidomycosis was confirmed by positive complement fixation and sputum culture. Tuberculosis was confirmed

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TABLE 1

CASES TREATED BY PULMONARY RESECTION

CASE	AGE	SEX	RACE	COCCIDIOIDES DIAGNOSIS CONFIRMED BY	TUBERCULOSIS DIAGNOSIS CONFIRMED BY	TREATMENT	PATHOGENESIS	PRESENT STATUS
1. F. T.	32	F	W	Culture of sputum; complement fixation	Culture of sputum	Right and left pneumothorax; right and left phrenic crush; pneumoperitoneum; right pneumonectomy	S 1	Full - time housework
2. G. J.	35	F	W	Spherules in surgical specimen	Surgical specimen and culture of sputum	Bed rest; left upper segmental resection	S 1	Full - time work; newspaper reporter
3. J. M.	31	M	W	Culture of sputum; complement fixation	Culture of sputum	Bed rest 16 months; right pneumothorax; pneumoperitoneum; right phrenic crush; right lower lobectomy	S 6	Full - time work; teaching school
4. I. U.	45	F	W	Spherules in surgical specimen	Culture of sputum	Bed rest; right pneumothorax; right pneumonolysis; right upper lobectomy and decortication	S 4	Full - time housework
5. J. A.	34	M	W	Spherules in surgical specimen; culture of sputum	Culture of sputum	Bed rest; 14 months in sanatorium; left pneumonectomy	S 1	Full - time work; personnel department, factory
6. M. H.	38	F	W	Complement fixation	Culture of sputum	Bed rest sanatorium and home 3½ years; left pneumothorax; attempted left pneumonolysis; left pneumonectomy	S 3	Negative; full-time housework
7. E. G.	62	F	W	Spherules in surgical specimen	Culture of sputum; tuberculous empyema	Bed rest; multiple aspirations; right pneumothorax; right middle lobectomy	S 3	Negative; housework

8. E. C.	29	M	Mexican	Culture of sputum	Clinical and roentgenographic proof of tuberculosis prior to coccidioidomycosis in contralateral lung	Bed rest; segmental resection right upper lobe	*6	Working full time
9. D. U.	43	M	W	Culture of sputum and bronchial secretions	Gastric washings	Left segmental resection upper lobe	*5	Working full time

TABLE 2A

PEDIATRIC MEDICAL CASES UNDER OBSERVATION

CASE	AGE	SEX	RACE	COCCIDIOIDES DIAGNOSIS CONFIRMED BY	TUBERCULOSIS DIAGNOSIS CONFIRMED BY	TREATMENT	PATHOGENESIS	PRESENT STATUS
1. H. G.	5	F	W	Skin test; complement fixation	Skin test; gastric washings and guinea pig inoculation	Antimicrobials and bed rest	4	Going to school; under observation
2. E. S.	2	M	N	Skin test; complement fixation	Skin test; gastric washings and guinea pig inoculation	Antimicrobials	4	Under observation, outpatient
3. V. G.	6	F	Mexican	Skin test; complement fixation	Skin test; gastric washings	Antimicrobials and bed rest	5	Under observation, outpatient
4. M. C.	13	F	Mexican	Skin test, sputum and culture; erythema nodosum	Sputum and culture	Antimicrobials and bed rest	5	In sanatorium
5. E. S.	7 months	M	N	Skin test; complement fixation	Guinea pig inoculation	Antimicrobials and bed rest	5	Under observation, outpatient
6. T. R.	2	M	Mexican	Skin test; complement fixation	Skin test; gastric washings and guinea pig inoculation	Antimicrobials and bed rest	6	In sanatorium
7. B. D.	9	F	N	Complement fixation	Gastric washings	Antimicrobials and bed rest	6	In sanatorium
8. O. R.	13	F	Chinese	Complement fixation	Gastric washings and guinea pig inoculation	Bed rest	6	In sanatorium

TABLE 2*B*

ADULT MEDICAL CASES UNDER OBSERVATION

CASE	AGE	SEX	RACE	COCCIDIOIDES DIAGNOSIS CONFIRMED BY	TUBERCULOSIS DIAGNOSIS CONFIRMED BY	TREATMENT	PATHOGENESIS	PRESENT STATUS
1. D. R.	24	F	W	Complement fixation; skin test	Culture of sputum	Left pneumothorax; bed rest; pneumoperitoneum	5	On pneumoperitoneum; no evidence of cavity
2. M. R.	45	M	Oriental	Complement fixation	Culture of sputum	Bed rest	5	Under observation; outpatient
3. J. M.	37	M	Mexican	Skin test; complement fixation	Skin test; culture of sputum and smear	Antimicrobials and bed rest	5	In sanatorium
4. B. C.	38	F	W	Skin test; complement fixation	Culture of sputum; cervical gland	Bed rest in sanatorium; left pneumothorax	1	Completely bedridden
5. F. C.	25	M	W	Complement fixation	Culture of sputum	Bed rest; antimicrobials	5	On pneumoperitoneum; in sanatorium
6. A. J.	22	F	W	Complement fixation	Gastric washings	Bed rest	3	In sanatorium
7. R. B.	50	M	W	Culture of sputum	Culture of sputum; guinea pig inoculation	Bed rest	5	In sanatorium

TABLE 3

CASES FROM LITERATURE

CASE OF	AGE	SEX	RACE	COCCIDIOIDES DIAGNOSIS CONFIRMED BY	TUBERCULOSIS DIAGNOSIS CONFIRMED BY	TREATMENT	PATHOGENESIS	PRESENT STATUS
Hyde and Hyde	21	M	Japanese	Spherules in skin abscess	Gastric washings	Penicillin and sulfa drugs	3	Dead
Firestone and Benson	34	M	W	Complement fixation; culture of sputum; spherules in skin lesion	Culture of sputum	Sulfa drugs; typhoid vaccine; X-ray therapy	History insufficient 6?	Dead
Morgenstern and Study	24	M	N	Culture of sputum; complement fixation	Culture of sputum	Right phrenic crush	1	Irregular discharge
Kahn	52	M	Oriental	Culture of sputum; complement fixation; guinea pig inoculation	Culture of sputum and smear	Bed rest; streptomycin, penicillin, sulfa drugs	5	Living and well
Stein*	34	M	N	Spherules found at autopsy	Culture of sputum	Streptomycin and PAS; pneumoperitoneum; phrenic crush	2	Died
	26	M	N	Culture of sputum	Culture of sputum	Bed rest	5	Irregular discharge
	56	M	W	Culture of sputum	Culture of sputum	Streptomycin and PAS	4	Not stated
	35	M	W	Culture of sputum	Culture of sputum	Bed rest; streptomycin and PAS; pneumoperitoneum	1	Not stated
	51	F	W	Culture of sputum	Gastric washings	Bed rest	1	Not stated
	39	M	W	Culture of sputum; surgical specimen	Culture of sputum; surgical specimen	Bed rest; streptomycin and PAS; pneumothorax; left upper lobectomy; thoracoplasty and decortication	1	Living and well

* Nine other cases reported but not in detail.

by culturing tubercle bacilli from gastric washings or sputum. Five patients are still in hospitals and 2 are under observation as outpatients. The treatments used consisted of pneumothorax, pneumoperitoneum, antimicrobials, and bed rest.

Ten cases reported in the literature are summarized in detail in table 3. Nine other cases were reported but not in detail. The patients ranged in age from twenty-one to fifty-six years. There were five whites, three Negroes, one Oriental, and one Japanese. Coccidioidomycosis and tuberculosis were confirmed by the previously reported laboratory methods. Only one patient was treated by surgery. The present status of most of these patients is not known.

Postulated Pathogenesis

The pathogenesis of coexisting pulmonary coccidioidomycosis and tuberculosis might conceivably take the following form:

Coccidioidal cavity with secondary infection by tuberculosis
Tuberculous cavity with secondary infection by *Coccidioides immitis*
Coccidioidal cavitation or infection in an area of dormant tuberculosis (1)
Tuberculous cavitation in an area of coccidioidal granuloma (2)
Concomitant infection (simultaneous infection with *Mycobacterium tuberculosis* and *Coccidioides immitis*); or
Coincident infection (separate area of pulmonary tissue involvement at different dates)

Diagnosis

The coexistence of various types of fungal diseases is not as rare as is generally believed. This is also true of coexisting tuberculosis and fungal diseases.

As illustrated by *Case 1* (table 1, figure 1*B*), when coccidioidal cavity is present and spread of the lesion occurs, coexisting secondary infection which can be caused by *Mycobacterium tuberculosis* should be suspected. In an established residual chronic cavity, an infiltrative process is not to be regarded as an exacerbation of coccidioidomycosis. A new etiologic agent must be sought. In the present cases, tuberculosis was a most common offender.

The converse is also true. If a patient with arrested pulmonary tuberculosis shows signs and symptoms typical of reactivation, especially if the patient is living in an area in which coccidioidomycosis is endemic, tuberculosis should not be assumed to be the etiologic factor until the presence of coccidioidomycosis has definitely been excluded. This type of instance is exemplified by figure 2*A*.

Carcinoma must be considered in the event that the pathologic process assumes a nodular appearance in the region of a previously resolving or stable pulmonary coccidioidomycosis or when hilar adenopathy persists.

In more than fifty cases of coccidioidal meningitis at Kern General Hospital during the past few years, there has been no instance in which the coccidioidal meningitis occurred after the development of a residual coccidioidal cavity. Consequently, once the diagnosis of coexisting coccidioidomycosis and tuberculosis has been established, meningitis which develops in a patient with a

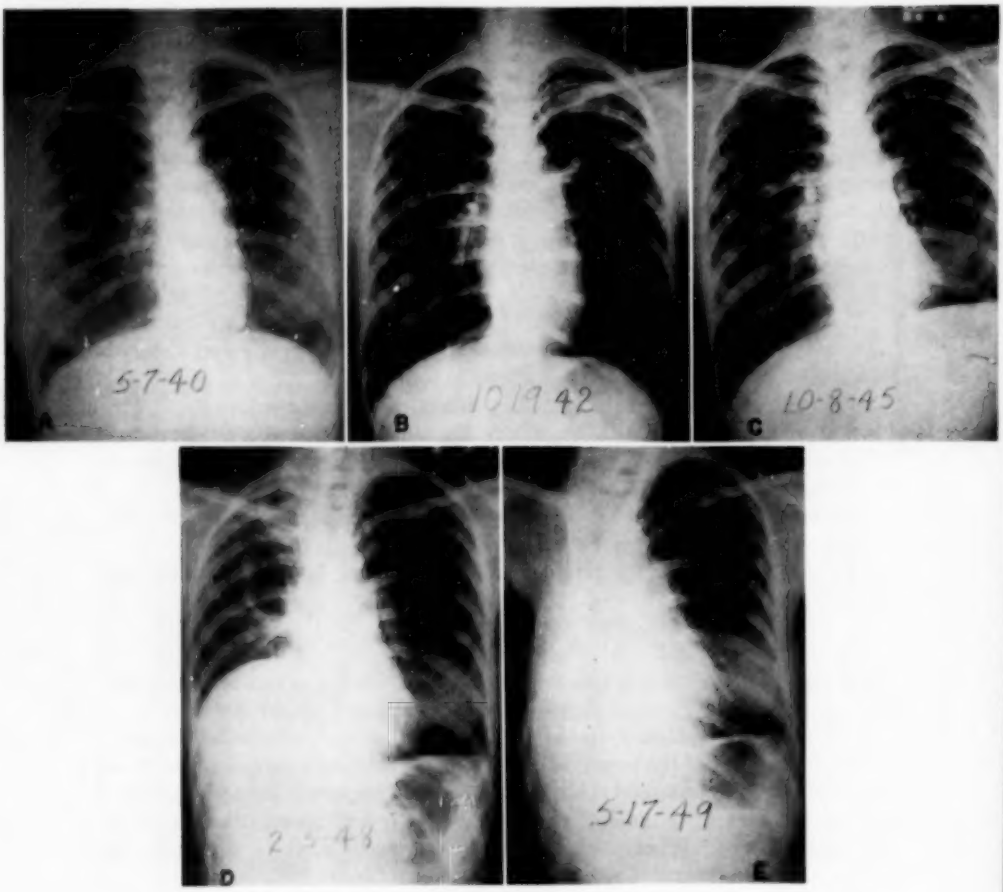

FIG. 1. *Case 1*

A. Proved coccidioidal cavity in right hilar area.

B. Secondary infection of coccidioidal cavity with tuberculosis with extension to left upper lung field.

C. Spread of tuberculosis controlled by left pneumothorax and phrenic nerve crush.

D. Tuberculous cavitation in right apex with enlargement of hilar cavity. Right phrenic nerve crush did not control the spread of the disease.

E. Right pneumonectomy and thoracoplasty. Patient working full time three years after surgery. Film taken one year after surgery shows no reactivation of disease.

pre-existing coccidioidal cavity can almost safely be assumed to be tuberculous in origin.

If a residual chronic cavity is under observation and a pleural effusion develops, tuberculosis should be suspected as the etiologic factor, since coccidioidal infections (in the experience of the present writers) do not reactivate.

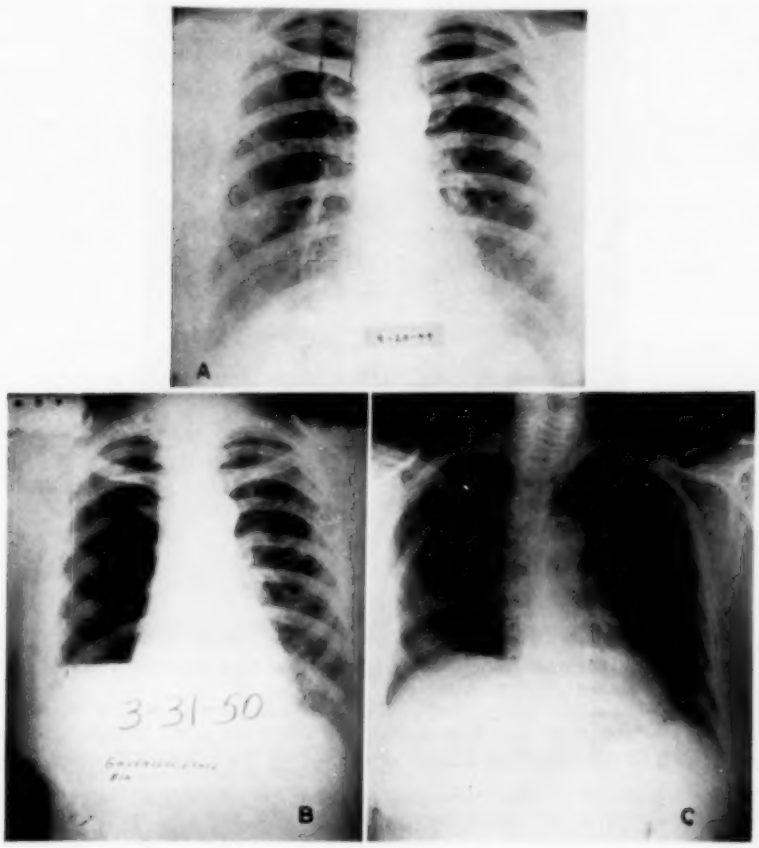

FIG. 2. *Case 7*

A. Pulmonary tuberculosis of right lung with area of density in lower lung field.
B. Right empyema with complete collapse of right lung.
C. Postoperative film after right decortication and right middle lobectomy.

A complete history is important in the differential diagnosis of pulmonary coccidioidomycosis and tuberculosis. Failure of the physician to obtain a history of the patient's activities while on holiday, as well as an occupational history, is a frequent source of misdiagnosis.

The differentiation of coccidioidal and tuberculous cavities may be difficult. In a particular patient, one cavity may contain *Mycobacterium tuberculosis* while a coexisting cavity, anatomically and roentgenographically similar to the first, may contain both *Mycobacterium tuberculosis* and coccidioidal spherules. Differentiation of one type of cavity from the other is facilitated by the fact that the coccidioidal cavity is usually surrounded by a minimal zone of reaction in contradistinction to the tuberculous cavity, which usually exhibits a con-

FIG. 3. *Case 4.* Roentgenogram showing how extreme lung destruction can be caused by coexisting diseases.

siderable reaction zone. The final differential diagnosis in all instances is made by recovery of the offending microorganism or by complement fixation test.

Treatment

As shown in tables 1 and 2, 9 of the patients with coexisting pulmonary coccidioidomycosis and tuberculosis were subjected to pulmonary resection while the remainder are under medical observation. Nineteen patients reported in the literature received medical therapy; one received pulmonary resection.

Case 1 (table 1) illustrates the successful management of the coexisting diseases by surgical means. Prior to pulmonary resection, this patient was treated medically over a period of ten years; during this preoperative period all feasible medical measures were employed including several forms of collapse therapy (except thoracoplasty).

In the present series, coccidioidal cavities secondarily infected with tuberculosis were not amenable to collapse therapy. This situation may be considered as constituting an indication for resection.

SUMMARY

A series of 24 cases of coexisting pulmonary coccidioidomycosis and tuberculosis is reported which has been assembled from the writers' experience and from the literature.

All but one of the coexisting cases of pulmonary coccidioidomycosis and tuberculosis reported in the literature were treated non-surgically. Nine of the patients in the present series were treated by pulmonary resection. In none of these 9 patients did spread of the infection occur postoperatively.

Coccidioidal cavities secondarily infected by *Mycobacterium tuberculosis* are seldom amenable to collapse therapy. In the presence of both diseases, the treatment of choice would seem to be pulmonary resection.

The possibility of coexisting pulmonary coccidioidomycosis and tuberculosis must be considered in the diagnosis of all pulmonary cavities.

If chronic coccidioidal cavitation is present and infiltration occurs, a secondary infection, usually tuberculosis, is the most common cause of the new area of disease.

The presence of coccidioidomycosis must definitely be excluded in patients who live in areas in which coccidioidomycosis is endemic and who show signs and symptoms of apparent reactivation of arrested tuberculosis.

Carcinoma should be suspected if nodular densities are noted in the presence of a coccidioidal cavity.

Meningitis appearing in a patient with a known coccidioidal cavity should be assumed to be tuberculous in etiology.

If pleural effusion occurs in a patient with a chronic coccidioidal cavity, tuberculosis is the most likely etiologic agent.

If a hydropneumothorax occurs, one must suspect rupture of the coccidioidal cavity.

SUMARIO

Coexistencia de Coccidioidomicosis y Tuberculosis Pulmonares

Preséntase una serie de 24 casos de coccidioidomicosis y tuberculosis pulmonares coexistentes a la par que se repasa la literatura pertinente.

Con excepción de uno, todos los casos de coexistencia de coccidioidomicosis y tuberculosis pulmonares comunicados hasta la fecha por otros autores fueron tratados médicamente. Nueve de los enfermos de los AA. fueron atendidos con la resección pulmonar, sin que en ninguno de ellos hubiera propagación postoperatoria de la infección.

Las cavernas coccidioideas infectadas secundariamente por el *Mycobacterium tuberculosis* rara vez ceden a la colapsoterapia. Cuando coexisten ambas dolencias, el tratamiento de elección parece ser la resección pulmonar.

En el diagnóstico de todas las cavernas pulmonares, hay que considerar la posible coexistencia de coccidioidomicosis y tuberculosis.

Si existe cavitación coccidioidal crónica y sobreviene infiltración, la causa más común de la propagación es una infección secundaria, por lo general tuberculosis.

Hay que excluir definitivamente la coccidioidomicosis en los enfermos que viven en zonas donde esa dolencia es endémica y que revelan signos y síntomas de aparente reactivación de una tuberculosis estacionada.

Debe sospecharse carcinoma si se notan densidades nodulares cuando existe una caverna coccidioidal.

Cabe suponer que la etiología es tuberculosa en toda meningitis que aparezca en un enfermo que se sabe tiene una caverna coccidioidal.

Si se presenta derrame pleural en un sujeto que tiene una caverna coccidioidal crónica, la tuberculosis es el agente etiológico más probable.

Si aparece hidroneumotórax, debe sospecharse rotura de la caverna coccidioidal.

RESUME

Coexistence de coccidiomycose pulmonaire et de tuberculose

Rapport sur une série de 24 cas où la coccidiomycose et la tuberculose coexistaient; les communications sur ce sujet sont passées en revue.

Jusqu'à ce jour, tous les cas d'association de la coccidiomycose pulmonaire et de la tuberculose sauf un, rapportés par d'autres auteurs, avaient été traités médicalement. Neuf des malades suivis par l'auteur ont été traités par la résection pulmonaire. Parmi ces neuf malades il ne s'est produit aucune dissémination post-opératoire de l'infection.

Les excavations coccidiales secondairement infectées par le *Mycobacterium tuberculosis* cèdent rarement au collapsus pulmonaire. En présence de ces deux affections il semble donc que le traitement de choix soit la résection pulmonaire.

La possibilité de la coexistence d'une coccidiomycose pulmonaire et de la tuberculose doit être envisagée dans le diagnostic de toute caverne pulmonaire.

En présence d'une caverne coccidiale chronique, l'apparition d'un infiltrat à ce niveau indique une infection secondaire; la tuberculose étant la cause la plus habituelle de cette contamination.

Le diagnostic de coccidiomycose doit être éliminé de façon absolue chez les patients habitant les régions où la coccidiomycose est endémique et qui présentent les manifestations pathologiques de la réactivation d'une tuberculose stabilisée.

Le diagnostic de cancer devra être considéré si des opacités nodulaires sont observées lorsqu'il existe une excavation coccidiale.

L'apparition d'une méningite chez un malade porteur d'une caverne coccidiale doit faire soupçonner l'étiologie tuberculeuse.

S'il se produit un épanchement pleural chez un malade porteur d'une caverne coccidiale chronique, la tuberculose est l'agent étiologique le plus probable.

S'il se produit un hydropneumothorax, il y a lieu de penser qu'il s'agit d'une caverne coccidiale rompue.

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ANTITUBERCULOUS ACTIVITY OF SUBSTITUTED THIOUREAS[1]

II. Activity in Mice

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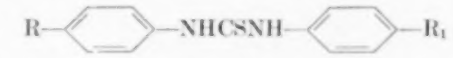
INTRODUCTION

Previous reports (1, 2) have indicated that certain diphenyl thioureas (thiocarbanilides) of the general structure:



have appreciable chemotherapeutic activity in tuberculous mice and guinea pigs. This paper presents data on the antimicrobial activity of more than 300 thiourea derivatives which were tested against *M. tuberculosis in vitro* and in mice.

OBSERVATIONS

In Vitro Tests

All compounds subjected to chemotherapeutic tests were also evaluated for *in vitro* activity against *M. tuberculosis* var. *hominis* (H37Rv) in a modified Kirchner's liquid medium[2] containing 0.03 per cent Tween® 80 and 0.5 per cent serum albumin. The test organism was grown in this medium for seven days at 37°C., and the resulting culture was then diluted with Kirchner's medium (without serum albumin) to contain approximately 50,000 organisms per ml. Inocula of 0.1 ml. amounts of diluted culture were used to seed 10 ml. of broth containing varying concentrations of the thioureas. Propylene glycol was used to prepare initial solutions of the more insoluble compounds. All assay tubes were incubated for fourteen days, and the minimal inhibiting concentrations were then determined.

The results of the *in vitro* testing of 295 thiourea derivatives showed considerable variation.[3] The minimal inhibiting concentration obtained with a number

[1] From the Research Department, CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

[2] Composition of modified Kirchner's medium

$Na_2HPO_4 \cdot 7H_2O$	3.0 gm.
KH_2PO_4	4.0 gm.
$MgSO_4$(anhyd)	0.6 gm.
Sodium citrate	2.5 gm.
Asparagine	5.0 gm.
Iron ammonium citrate	0.05 gm.
Glycerin	20.0 ml.
Tween® 80	0.3 ml.
Distilled water, q.s.	1,000 ml.

Autoclave for fifteen minutes at 15 pounds. Sterile (Seitz-filtered) serum albumin solution is then added.

[3] The *in vitro* activities of these compounds are recorded in the appendix tables in the reprints of this article.

TABLE 1

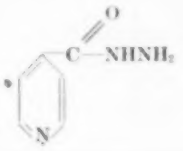
RELATIONSHIP BETWEEN THE IN VITRO AND IN VIVO ACTIVITIES OF 307 THIOUREAS

MINIMAL INHIBITING CONCENTRATION IN BROTH	NUMBER OF COMPOUNDS (TOTAL)	NUMBER OF COMPOUNDS		
		With Significant Activities *in Vivo*	Per Cent	Inactive *in Vivo*
γ per ml.				
1	27	27	100	0
2–5	42	32	76	10
6–10	28	17	50	11
11–30	100	33	33	67
31–100	87	21	22	66
>100	23	3	13	20

TABLE 2

ANTITUBERCULOUS ACTIVITIES IN MICE OF SELECTED THIOUREAS

R—HNCSNH—R′

COMPOUND	STRUCTURE		PER CENT CONCENTRATION IN DIET	INCREASE IN T_{50} VALUE OVER CONTROLS (DAYS)	PER CENT SURVIVORS
	R	R′			
Su 1795	C_2H_5O-	$-OCH_2CH(CH_2)_2$	0.10	15.0 +	100
			0.05	15.0 +	70
			0.025	−1.0	0
Su 1906	$CH_3(CH_2)_2O-$	$-N(CH_3)_2$	0.05	16.0 +	100
			0.025	16.0 +	80
			0.01	1.0	10
Su 2079 HCl	$CH_3(CH_2)_2O-$	$-OCH_2CH_2N(C_2H_5)_2$	0.05	15.0 +	90
			0.025	15.0 +	90
			0.01	2.0	20
Su 2358 HCl	$(CH_3)_2CHCH_2O-$	$-OCH_2CH_2N(C_2H_5)_2$	0.05	15.0 +	100
			0.025	15.0 +	90
			0.01	0.0	0
Isoniazid			0.025	15.0 +	100
			0.01	15.0 +	100
			0.005	15.0 +	100

of these compounds was 1 γ per ml., whereas many others were active only at a concentration of 125 γ per ml. There was no correlation, however, between the *in vitro* and *in vivo* results, for certain compounds with appreciable activities in mice possessed relatively low *in vitro* activities (table 1). Four of the thioureas which exerted excellent therapeutic effects in mice infected with the H37Rv

TABLE 3

IN VITRO ANTIMYCOBACTERIAL ACTIVITIES OF CHEMOTHERAPEUTICALLY ACTIVE THIOUREAS AND OTHER SUBSTANCES

TEST ORGANISM	MINIMAL INHIBITING CONCENTRATIONS (γ PER ML.) OBTAINED WITH THE FOLLOWING SUBSTANCES:					
	Thioureas*				Isoniazid	Streptomycin
	Su 1795	Su 1906	Su 2079	Su 2358		
M. tuberculosis						
Human strains:						
H37Rv #80	2.0	2.0	16.6	16.6	<0.5	4.0
H37Rv #164	2.0	3.9	16.6	31.3	<0.5	3.9
H37Rv #301	3.9	3.9	125.0	31.3	<0.5	0.5
H37Rv #302	2.0	2.0	62.5	31.3	<0.5	0.5
H37Rv #225†	7.8	3.9	125.0	62.5	<0.5	1.0
Bovine strains:						
Ravenel #226	3.9	2.0	16.6	16.6	<0.5	4.0
#76	16.6	7.8	62.5	31.3	<0.5	4.0
BCG #256	31.3	16.6	31.3	31.3	<0.5	2.0
M. avium #299	31.3	2.0	16.6	62.5	7.5	4.0
Saprophytic mycobacteria						
M. lacticola #126	31.3	31.3	125.0	62.5	0.5	62.0
M. phlei #42	125.0	125.0	125.0	62.5	1.0	4.0
M. smegmatis #63	31.3	125.0	125.0	125.0	2.0	4.0
M. stercoris #40	125.0	125.0	62.5	62.5	1.0	2.0
M. berolinense #46	125.0	125.0	62.5	62.5	1.0	4.0

* The chemical structures of these compounds are given in table 2.

† This strain was used for all routine *in vitro* assays

strain (table 2) were selected for *in vitro* testing against a variety of pathogenic and saprophytic acid-fast organisms and the observed minimal inhibiting concentrations are recorded in table 3.

In Vivo Tests

Screening for antituberculosis activity: In the initial phase of the study, the substances subjected to evaluation were tested in mice infected with the Ravenel (bovine) strain of *M. tuberculosis*, utilizing a technique similar to that described by Donovick, Rake, and co-workers (3, 4). Although untreated mice infected intravenously with a standardized inoculum of this strain succumbed at a relatively uniform rate, the use of the Ravenel strain was not entirely satisfactory. The tuberculous lesions which developed in the lungs of mice treated with adequate doses of streptomycin, para-aminosalicylic acid, or amithiozone approached in intensity those observed in the untreated groups in spite of a marked prolongation in survival rates. In subsequent experiments, the bovine strain was replaced by the H37Rv strain which yielded, under standard conditions, a predictable mortality rate for the untreated animals as well as the development of lung lesions more amenable to the influence of the above-mentioned therapeutic agents. However, in agreement with the observation made by Rake and associates (4), the

measurement of lung lesion involvement in mice, as advocated by Raleigh and Youmans (5, 6, 7), was considered of lesser importance in a preliminary screening program than criteria based upon survival rates.

White (CF_1) mice, weighing between 15 and 20 gm., were infected intravenously in the tail vein with 0.5 ml. amounts of a culture grown for seven days in Kirchner's liquid medium containing 0.03 per cent Triton-A20 and 0.5 per cent serum albumin and then diluted approximately tenfold to standard turbidity. The organism was maintained in a uniformly virulent state by periodic reisolations from rough, corded colonies.

With but few exceptions, all substances were administered to mice admixed in finely ground Rockland mouse diet immediately following infection, and the treatment was maintained for thirty consecutive days. The experiments were terminated fifteen days beyond that day, as calculated, when 50 per cent of the untreated animals succumbed to the infection (T_{50}).

The infecting dose used in 43 consecutive experiments performed with the Ravenel strain was such that the average T_{50} value for the untreated groups was 19.0 days (plus-minus 2.7). Later, when this culture was replaced by the H37Rv strain, the average T_{50} value obtained in the first 12 experiments was 19.8 days with a standard deviation of plus-minus 1.6 days. Thus, in an experiment yielding a T_{50} value of 20 days for the untreated group, all surviving mice were sacrificed on the thirty-fifth day.

In the diet experiments, all compounds were incorporated into the mouse diet at the maximal acceptable concentration, but in no instance, except for sulfanilyl thiourea, was the concentration greater than 0.5 per cent.

The compounds which demonstrated excellent activities (T_{50} values of thirty-five days) by this procedure were further tested at decreasing levels in order to establish the minimal effective doses. In these graded dose experiments, medicated food was supplied to the infected mice immediately after infection as in the preliminary evaluations, but therapy was maintained for a total of only twenty-one consecutive days. Unmedicated mouse food was then restored and all surviving animals were sacrificed on the thirty-fifth day post infection.

From among the many thioureas thus evaluated, 91 were found to yield T_{50} values of at least thirty-five days. Since a complete listing of the activities of all compounds tested would render this report too voluminous, only the active thioureas are recorded.[4]

Active Thioureas (T_{50} Values of Thirty-five Days) and Corresponding Concentrations in the Diet

Monosubstituted thioureas:

sulfanilylthiourea, 2.0 per cent

1,3-Disubstituted thioureas:

a. R—NHCSNH—R (symmetrical)

R: 4-C_2H_5O—C_6H_4—, 0.1%; 4-n-C_3H_7O—C_6H_4—, 0.05%; 4-iso-C_3H_7O—C_6H_4—, 0.01%; 4-n-C_4H_9O—C_6H_4—, 0.025%; 4-sec-C_4H_9O—C_6H_4—, 0.05%; 4-iso-C_4H_9O—C_6H_4—, 0.01%; 4-n-$C_5H_{11}O$—C_6H_4—, 0.05%; 4-iso-$C_5H_{11}O$—C_6H_4—, 0.025%; 4-(CH_2=$CHCH_2O$)—C_6H_4—, 0.01%; 4-$CH_3CH_2OCH_2$-CH_2O—C_6H_4—, 0.05%; 4-n-C_3H_7O—C_6H_4—, 0.025%; 4-n-C_4H_9—C_6H_4—, 0.1%; 4-n-C_5H_{11}—C_6H_4—, 0.05%; 4-iso-C_5H_{11}—C_6H_4—, 0.025%; 4-CH_3-

[4] Details of the results obtained with each of the thioureas investigated are available in the appendix tables in the reprint of this article.

OCH_2CH_2—C_6H_4—, 0.025%; 4-$CH_3OCH_2CH_2CH_2$—C_6H_4—, 0.25%; 4-$(C_2H_5)_2N$—C_6H_4—, 0.3%; 4-CH_2O—$C_6H_4CH_2$—, 0.5%; 3-(6-n-butoxypyridyl)-, 0.5%

b. 4-C_2H_5O—C_6H_4—NHCSNH—R

R: 4-F—C_6H_4—, 0.5%; 4-I-C_6H_4—, 0.5%; 4-iso-C_3H_7—C_6H_4—, 0.5%; 4-n-C_4H_9—C_6H_4—, 0.05%; 4-tert-C_4H_9—C_6H_4—, 0.5%; 4-n-C_5H_{11}—C_6H_4—, 0.1%; 4-iso-C_5H_{11}—C_6H_4—, 0.05%; 4-n-C_6H_{13}—C_6H_4—, 0.2%; 4-$CH_2CH_2OCH_2$—C_6H_4—, 0.3%; 4-$CH_3OCH_2CH_2$—C_6H_4—, 0.05%; 4-HO—C_6H_4—, 0.5%; 4-CH_3O—C_6H_4—, 0.25%; 4-n-C_3H_7O—C_6H_4—, 0.05%; 4-iso-C_3H_7O—C_6H_4—, 0.05%; 4-n-C_4H_9O—C_6H_4—, 0.1%; 4-iso-C_4H_9O—C_6H_4—, 0.05%; 4-sec-C_4H_9O—C_6H_4—, 0.05%; 4-n-$C_5H_{11}O$—C_6H_4—, 0.05%; 4-iso-$C_5H_{11}O$—C_6H_4—, 0.025%; 4-n-$C_6H_{13}O$—C_6H_4—, 0.5%; 4-n-$C_7H_{15}O$—C_6H_4—, 0.5%; 4-C_6H_5O—C_6H_4—, 0.5%; 4-C_5H_9O—C_6H_4—, 0.5%; 4-$HOCH_2CH_2O$—C_6H_4—, 0.05%; 4-$C_2H_5OCH_2CH_2O$—C_6H_4—, 0.1%; 4-CH_3CH_2CO—C_6H_4—, 0.5%; 4-$CH_3OCH_2CH_2CH_2$—C_6H_4—, 0.1%; 2,3-(Cl)(C_2H_5O)—C_6H_4—, 0.5%; 4-$(CH_3)_2N$—C_6H_4—, 0.025%; 4-$(C_2H_5)_2N$—C_6H_4—, 0.05%; 4-(n-$C_4H_9)_2N$—C_6H_4—, 0.05%; 4-C_6H_5NH—C_6H_4—, 0.5%; 4-$(C_2H_5)_2NCH_2CH_2O$—C_6H_4—, 1.0 mg. per os; 4-$(CH_3)_2NCH_2CH_2O$—C_6H_4—, 0.1%; 3,4-$(CH_3CONH)(C_2H_5O)$—C_6H_3—, 0.5%; 4-$(C_2H_5)_2NCH_2CH_2O$—C_6H_4—, 4-C_2H_5S—C_6H_4—, 0.5%; 4-n-C_3H_7S—C_6H_4—, 0.3%; 4-$C_2H_5OCH_2CH_2S$—C_6H_4—, 0.5%; 4-$(C_2H_5)_2NCH_2CH_2S$—C_6H_4—, 0.5%; 4-iso-$C_5H_{11}S$—C_6H_4—, 0.5%; 4-$C_2H_5SCH_2CH_2O$—C_6H_4—, 0.5%; 4-(1-piperidyl)-, 0.05%; 3-quinolyl-, 0.25%; 4-CH_3O—C_6H_4—CH_2—, 0.5%.

c. 4-n-C_3H_7O—C_6H_4—NHCSNH—R

R: 4-Br—C_6H_4—, 0.1%; 4-Cl—C_6H_4—, 0.05%; 4-F—C_6H_4—, 0.3%; 4-I—C_6H_4—, 0.1%; 4-CH_3—C_6H_4—, 0.5%; 4-n-C_4H_9—C_6H_4—, 0.025%; 4-n-$C_6H_{11}O$—C_6H_4—, 0.025%; 4-$(CH_3)_2N$—C_6H_4—, 0.025%; 4-n-$(C_2H_5)_2N$—C_6H_4—0.1%; 4-$(C_2H_5)_2NCH_2CH_2O$—C_6H_4—, 0.025%.

d. 4-Cl—C_6H_4—NHCSNH—R

R: 4-n-C_4H_9—C_6H_4—, 0.5%; 4-n-C_3H_7O—C_6H_4—, 0.1%; 4-iso-C_3H_7O—C_6H_4—, 0.5%; 4-n-$C_5H_{11}O$—C_6H_4—, 0.5%; 4-n-$C_7H_{15}O$—C_6H_4—, 0.5%; 4-$(CH_2{=}CHCH_2O)$—C_6H_4—, 0.05%; 4-C_6H_5O—C_6H_4—, 0.5%.

e. R—NHCSNH—R′ (miscellaneous)

4-n-C_4H_9—C_6H_4—	4-$(CH_3)_2N$—C_6H_4—	0.05%
4-n-C_4H_9—C_6H_4—	4-$(C_2H_5)_2NCH_2CH_2O$—C_6H_4—	0.05%
4-n-C_3H_7O—C_6H_4—	4-$(CH_3)_2N$—C_6H_4—	0.025%
4-iso-C_4H_9O—C_6H_4—	4-$(CH_3)_2N$—C_6H_4—	0.025%
4-iso-C_4H_9O—C_6H_4—	4-$CH_3OCH_2CH_2CH_2$—C_6H_4—	0.025%
4-iso-C_4H_9O—C_6H_4—	4-$(C_2H_5)_2NCH_2CH_2O$—C_6H_4—	0.025%
4-n-$C_5H_{11}O$—C_6H_4—	4-$(C_2H_5)_2N$—C_6H_4—	0.1%
4-iso-$C_5H_{11}O$—C_6H_4—	4-$(CH_3)_2N$—C_6H_4—	0.025%

Trisubstituted thioureas:

RR′NCSNHR″

R: CH_3CO—; R′: 4-C_2H_5O—C_6H_4—; R″: 4-C_2H_5O—C_6H_4—, 0.5%.

Limited and delayed therapy experiments: In order to establish further the degree of activity of the more interesting compounds, treatment of groups of infected mice was limited to only one, two, three, six, nine, and twelve days, respectively (table 4). In another series of experiments, treatment of infected mice was delayed for various periods of time up to twelve days after infection, but in each instance was maintained for a total of twenty-one consecutive days (table 5). Both types of experiments were terminated on the thirty-fifth day post infection.

Evaluation of therapeutic activity: The estimation of the results of therapy in all experiments was based on the following criteria:

a. Extension of T_{50}—An increase in the T_{50} of three or more days beyond that obtained for the untreated, infected group was considered significant and therefore indicative of chemotherapeutic activity.

b. The per cent survival of mice within each treated group upon termination of the experiment.

TABLE 4

EFFECT OF DELAYED THERAPY WITH SELECTED THIOUREA DERIVATIVES ON MOUSE TUBERCULOSIS (H37Rv)

DELAY IN TREATMENT	INCREASE IN T_{50} (DAYS) OBTAINED WITH 0.05 PER CENT CONCENTRATIONS OF COMPOUND IN THE DIET		
	Su 1793	Su 1906	Su 2158
days			
0	13.5	15+	15+
3	13.0	15+	15+
6	0	15+	15+
9	0	15+	15+
12	0	8.0	0
15	0	3.0	0

TABLE 5

EFFECT OF LIMITED THERAPY WITH SELECTED THIOUREA DERIVATIVES ON MOUSE TUBERCULOSIS (H37Rv)

TOTAL TIME OF TREATMENT	INCREASE IN T_{50} (DAYS) OBTAINED WITH 0.1 PER CENT AND 0.05 PER CENT CONCENTRATION OF COMPOUND IN THE DIET					
	Su 1793		Su 1906		Su 2158	
	0.1 Per Cent	0.05 Per Cent	0.1 Per Cent	0.05 Per Cent	0.1 Per Cent	0.05 Per Cent
days						
1	—	—	0*	6.0	—	—
2	—	—	0*	15+	—	—
3	0	0	15+	15+	12.0	3.5
6	15+	4.0	15+	15+	15+	15+
9	15+	0	15+	15+	15+	15+
12	15+	15+	15+	15+	15+	15+

* Due to the unpalatability of the medicated diet containing the higher concentration of drug, a brief period of adjustment was necessary and the amount of food eaten during the first forty-eight hours of therapy was considerably below the normal food intake.

Resistance Studies

Attempts to produce, by serial transfer through broth, a strain of H37Rv resistant to representative thiourea derivatives have indicated that such resistance emerges at a slower rate than is encountered with streptomycin or isoniazid. Organisms isolated on several occasions from infected mice treated with thioureas were found to have developed no measurable degree of resistance.

By means of serial transfers through broth containing increasing concentrations of streptomycin, a strain of H37Rv was obtained which was capable of growth in the presence of 10 γ per milliliter of broth. Mice infected with the streptomycin-resistant strain thus obtained were treated with seven thiourea derivatives possessing excellent activities as determined in earlier experiments. The compounds were thoroughly incorporated in the ground food in concentrations of 0.05 and 0.1 per cent. Included in the experiment were diets prepared with amithiozone (0.05 and 0.1 per cent) and para-aminosalicylic acid (0.1 and 0.5 per cent). Two additional groups of mice were treated subcutaneously with 1.5 and 3.0 mg. of streptomycin respectively, administered daily. Groups of 10 mice were used for each dose level. In all instances, with the exception of streptomycin, treatment resulted in an extension of the T_{50} value of fifteen days beyond that obtained for the control group. Treatment with streptomycin, however, afforded no significant degree of protection, although the doses employed were highly effective against infection induced with a nonresistant strain. All organisms isolated from the lungs of mice treated with each of the substances employed were found to have retained their original degree of streptomycin resistance.

DISCUSSION

It is well known that, among the many classes of chemotherapeutically active compounds, a number of substances exert little, if any, appreciable activity by standard *in vitro* techniques. Examples of such substances are the arsphenamines, antimonials, and Prontosil. Conversely, a very large number of compounds are known to possess high *in vitro* activities but are completely devoid of any demonstrable chemotherapeutic effects in the animal body. For these reasons, all compounds screened for antituberculous activity were subjected to both the *in vitro* and *in vivo* tests. From the data obtained, several observations are evident.

Unlike the other antituberculous agents, such as streptomycin and isoniazid, which are active *in vitro* against a wide range of pathogenic and saprophytic mycobacteria, the substituted thioureas direct their activity only against the tubercle bacillus (table 3). The range of *in vitro* activities of these latter compounds extend from a low level (less than 125 γ per ml.) to a maximum of approximately 1 γ per ml., depending upon the organism tested.

Eighty-eight per cent of all compounds possessing an *in vitro* activity at a concentration of 5 or less γ per ml. of test medium were also active in mice. Thus, for the majority of thioureas studied, a direct relationship between the *in vitro* and *in vivo* activities (table 1) exists. On the other hand, 13 per cent of those sub-

stances essentially inactive *in vitro* (more than 100 γ per ml.) were nevertheless effective in tuberculous mice. Examples of compounds demonstrating a poor degree of correlation are *Su 2079* and *Su 2358* (tables 2 and 3). In spite of closely related chemical configuration, certain thioureas are either highly active *in vitro* and inactive in the mouse or, conversely, possess no appreciable activity *in vitro* but have significant activity *in vivo*.

Of the 11 representative monosubstituted and 1,1-disubstituted thioureas included in this study, only sulfanilyl-thiourea (8) exhibited any appreciable degree of *in vivo* activity, although it required a concentration of approximately 2.0 per cent in the diet to exert this effect. It is questionable whether the activity of this compound is due primarily to the thiourea component.

Ninety-five per cent of all compounds demonstrating significant *in vivo* activities were among the 1,3-disubstituted thioureas subjected to evaluation. An analysis of the chemical structures of these active compounds reveals that the substituents attached to the benzene rings must be located at the 4,4′ positions and that maximum activity is obtained when these substituents consist of 3 or 4 carbon atoms (2).

SUMMARY

Among a large number of substituted thioureas, 96 compounds demonstrated significant antituberculous activities in the experimentally infected mouse.

The large majority of these active compounds were 1,3-diphenyl thioureas bearing substituents on the benzene rings in the 4,4′ positions.

No clear-cut correlation was observed between the *in vitro* and *in vivo* activities.

Representative thiourea derivatives exerted undiminished activities when tested in mice infected with a streptomycin-resistant strain of *M. tuberculosis* H37Rv.

SUMARIO

Actividad Antituberculosa de las Tioureas Substituídas: II. Actividad en los Ratones

Entre una gran cantidad de tioureas substituídas, 108 compuestos mostraron importante actividad antituberculosa en ratones infectados experimentalmente.

La gran mayoría de esos compuestos activos eran 1,3-difenil-tioureas, que contenían substituyentes en los anillos bencénicos en las posiciones 4,4′.

No se observó correlación bien definida entre las actividades *in vitro* e *in vivo*.

Típicos derivados de la tiourea ejercieron sin atenuación sus actividades al ser comprobados en ratones infectados con una cepa estreptomicinorresistente de H37Rv.

RESUME

Activité antituberculeuse des thio-urées substituées: II. Activité chez la souris

Parmi un nombre important de thio-urées substituées, 108 composés ont démontré des propriétés antituberculeuses appréciables dans la tuberculose expérimentale de la souris.

La grande majorité de ces composés actifs étaient des 1,3-diphényl thio-urées avec substituants fixés aux cycles benzéniques en position 4,4′.

Aucune corrélation bien définie ne fut observée entre l'activité *in vitro* et *in vivo*.

L'activité des dérivés caractéristiques de la thio-urée, éprouvée chez des souris inoculée avec une souche H37Rv streptomycine-résistante, n'était pas diminuée.

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ANTITUBERCULOUS ACTIVITY OF SUBSTITUTED THIOUREAS[1]

III. Activity in Guinea Pigs

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INTRODUCTION

In previous reports, the antituberculous activity of certain diphenyl thioureas in experimentally infected mice was described in detail (1, 2), but only a brief account was given of their activity in the guinea pig. The present paper deals with the evaluation of these compounds in tuberculous guinea pigs.

The use of mice as test animals for the routine screening of substances for antituberculous activity undoubtedly offers many practical advantages, particularly when applied to large-scale programs. However, a number of workers (3, 4, 5) consider the guinea pig as a more realistic and appropriate test object. From a clinical and pathologic standpoint, guinea pig tuberculosis resembles the human disease in many respects, for example, in the production and localization of tuberculous lesions and in the development of a highly allergic state. Not only is this animal highly susceptible to infection by *M. tuberculosis*, but the course of the disease, as revealed by histopathologic examination of the involved organs, lends itself to a critical evaluation of the effectiveness of chemotherapeutic agents previously selected on the basis of preliminary mouse tests.

In view of the impressive activities of a number of thiourea derivatives in mice infected with either the Ravenel or H37Rv strains of *M. tuberculosis*, a series of experiments were performed in guinea pigs, several of the more active compounds being selected for these tests.

METHODS

Adult, female guinea pigs, ranging in weight between 500 and 600 gm., were injected subcutaneously in the left groin with 1.0 ml. of a 1:100 saline dilution of H37Rv culture grown for seven days in a modified liquid Kirchner medium (2). Approximately twenty-three days after infection, the animals were tuberculin-tested (0.1 ml. of a 1 per cent solution of Old Tuberculin (OT) intracutaneously) and all responded with a strong positive reaction. Treatment with the various thioureas was instituted immediately upon the completion of the tuberculin test with the exception of a delayed therapy experiment (Exp Bk. 12/19).

Finely ground, standard guinea pig diet containing the test substance previously pulverized to 200 mesh particle size was fed ad libitum. This medicated diet was supplemented with daily rations of fresh greens and ascorbic acid which was added to the drinking water (0.5 mg. per ml.) on alternate days. At the end of the treatment period, all surviving animals were sacrificed. The gross organ involvement was determined according to the procedure described by Feldman and Karlson (4, 6) by the assignment of numerical values for the spleen, lungs, and liver according to the extent of tuberculous involvement. As indicated in the following chart, maximal values of 40, 70, and 100, respectively, were given to animals with *slight*, *moderate*, and *extensive* degrees of total organ involvement.

[1] From the Research Department, CIBA Pharmaceutical Products, Inc., Summit, New Jersey; and the Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts.

SCHEME OF NUMERICAL EVALUATION OF MACROSCOPIC INVOLVEMENT

Degree of Involvement	Spleen	Lungs	Liver	Involvement at Site of Inoculation	Total Involvement
Maximum	35	30	25	10	100
Moderate	20	20	20	10	70
Slight	10	10	10	10	40

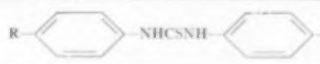
In two of the experiments (Exp. Bk. 5/266 and Exp. Bk. 12/19), histopathologic analysis of tuberculous involvement was included. A code was adopted to indicate the extent of disease observed in the spleen, lungs, and liver, assigning scores of 0, 8, 16, 25, and 33, respectively, for the various degrees of severity.

0 = no pathologic involvement
8 = questionable foci of mononuclear cells or fibroblastic cells not definitely creating a granuloma
16 = rare but definite tubercle formation, or very early tubercle formation without caseation necrosis
25 = occasional to moderate numbers of tubercles, well formed but with caseation necrosis or demonstrable acid-fast bacilli
33 = many tubercles, confluent tubercles, or tubercles with caseation necrosis; acid-fast bacilli present

As in the assessment of macroscopic involvement, the maximal value obtainable by this method of histologic scoring of the three involved organs is approximately 100.

EXPERIMENTAL

Exp. Bk. 5/266: Antituberculous activities of selected thioureas (table 1).

THIOUREAS TESTED		
	R	R'
Su 1380	C_2H_5O—	C_2H_5O—
Su 1705	n-C_3H_7O—	n-C_3H_7O—
Su 1795	C_2H_5O—	iso-C_4H_9O—
Su 1748	iso-$C_5H_{11}O$—	iso-$C_5H_{11}O$—
Su 2079	n-C_4H_9O—	$(C_2H_5)_2NCH_2CH_2O$—
Su 1814	n-C_4H_9—	n-C_4H_9—
Su 1906	n-C_3H_7—	$N(CH_3)_2$—

Treatment started: twenty-first day post infection.
Duration of treatment: 115 days.

As judged by the extent of macroscopic involvement, as shown in table 1, all of the compounds, with the exception of Su 1814, demonstrated considerable antituberculous activity. At the same dose levels, Su 1705 and Su 2079 exhibited activities approximately of the same order as isoniazid. On the basis of the histologic examinations, two of the compounds, Su 1795 (0.2 per cent) and Su 2079 (0.1 per cent) were particularly noteworthy in that they brought about virtually total regression of the tuberculosis and produced results equal to those obtained with isoniazid. Indeed, in the organs of the animals treated with these two substances, there was no residual evidence of caseation necrosis or proliferative

TABLE 1

EVALUATION OF THERAPY OF TUBERCULOUS GUINEA PIGS WITH SELECTED THIOUREAS

COMPOUND	PER CENT OF CONCENTRATION IN DIET	NUMBER OF ANIMALS	AVERAGE MACROSCOPIC INVOLVEMENT*					AVERAGE MICROSCOPIC INVOLVEMENT			
			Spleen	Lungs	Liver	Site of Inoculation	Total Involvement	Spleen	Lungs	Liver	Total Involvement
Su 1380	0.2	13	4.6	2.3	5.4	1.5	13.8	0	2.5	1.7	4.2
	0.05	12	5.8	5.0	6.7	5.8	23.3	0	2.3	3.0	5.3
Su 1705	0.2	13	4.6	0.8	3.8	1.5	10.8	0	0.6	0	0.6
	0.05	12	5.8	3.3	1.7	1.7	12.5	0	0	0	0†
Su 1748	0.2	14	2.1	5.0	5.0	2.9	15.0	—	—	—	—
	0.05	14	2.9	5.7	8.6	3.6	20.7	1.8	2.5	6.7	11.0
Su 1795	0.2	12	5.8	2.5	5.8	0.8	15.0	0	0	0	0
	0.05	14	7.2	8.6	7.9	1.4	25.0	1.3	2.1	4.1	7.5
Su 1814	0.2	14	13.6	13.6	10.7	6.4	44.2	8.9	12.5	13.7	35.1
	0.05	13	13.1	13.1	13.5	6.9	46.5	8.0	8.3	14.2	30.5
Su 1906	0.1	12	4.2	4.2	6.7	2.5	17.5	1.2	5.3	1.9	8.3
	0.05	10	2.0	4.0	6.0	4.0	16.0	4.2	0.3	4.2	8.7
Su 2079	0.1	15	0.7	2.0	1.3	2.7	6.7	0	0.8	0.3	1.1
	0.05	13	3.9	4.6	5.8	3.9	18.1	3.3	5.0	7.5	15.8
Isoniazid	0.1	13	1.5	1.5	2.3	0.8	6.2	0	0.7	0	0.7
	0.05	13	3.1	3.1	3.1	2.3	11.5	0.4	0	0	0.4
Amithiozone	0.1	12	2.5	7.5	9.2	5.0	24.2	0	5.5	11.8	17.3
	0.05	12	9.2	10.8	12.9	5.0	37.9	10.6	6.4	14.0	31.0
Untreated controls	—	13	23.7	25.2	24.2	10.0	83.5	18.1	17.2	17.2	52.5
Pretreatment controls‡	—	5	21.0	10.0	13.0	10.2	54.0	14.6	14.6	18.3	47.5

* Macroscopic involvement indices are higher than those obtained by microscopic examination because of the inclusion of lesions of nontuberculous origin.

† Based on evaluation of 3 animals.

‡ The pretreatment controls were sacrificed at the commencement of therapy (twenty-first day post infection) in order to establish the extent of tuberculous involvement.

tuberculosis. All of the tubercles showed varied stages of healing as evidenced by the accumulation of lymphocytes within the granulomatous focus and calcification of the centers of these tubercles.

Exp. Bk. 12/20: Antituberculous activities of selected thioureas (table 2).

THIOUREAS TESTED		
	R	R'
Su 1795	C_2H_5O—	iso-C_4H_9O—
Su 1906	n-C_4H_9O—	$N(CH_3)_2$—
Su 2358 (HCl)	iso-C_4H_9O—	$(C_2H_5)_2NCH_2CH_2O$—

Treatment started: twenty-second day post infection.
Duration of treatment: 60 days.

TABLE 2

EVALUATION OF THERAPY WITH SELECTED THIOUREAS

COMPOUND	PER CENT OF CONCENTRATION IN DIET	NUMBER OF ANIMALS	AVERAGE MACROSCOPIC INVOLVEMENT				
			Spleen	Lungs	Liver	Site of Inoculation	Total Involvement
Su 1795	0.05	15	5.3	10.0	2.0	4.7	22.0
	0.01	15	7.7	12.0	5.0	7.3	32.0
	0.005	13	6.5	6.9	5.0	6.9	26.0
Su 1906	0.05	14	4.2	5.0	8.9	5.0	23.1
	0.01	13	8.0	7.6	4.2	6.9	26.9
	0.005	14	18.5	15.7	12.1	8.5	55.0
Su 2358	0.05	14	6.0	8.5	3.5	7.8	26.0
	0.01	13	12.3	12.3	16.1	10.0	50.8
	0.005	12	18.3	14.1	15.8	8.3	57.0
Isoniazid	0.05	10	8.8	4.4	1.1	4.4	18.8
	0.01	15	8.6	7.3	5.6	5.3	27.0
	0.005	15	10.3	10.6	5.0	6.0	32.0
Controls	—	15	18.6	16.0	21.6	9.3	65.0
Pretreatment controls*	—	5	24.0	10.0	13.0	10.0	57.0

* These animals were sacrificed at the commencement of therapy (twenty-second day post infection).

Of the three thioureas tested and evaluated on the basis of macroscopic involvement, Su 1795 exhibited activities at each of the three dose levels tested (0.05, 0.01, and 0.005 per cent). As in the preceding experiment, the effectiveness of this substance was comparable to that of isoniazid. Su 1906, except for the lowest dose level tested (0.005 per cent), also proved to be effective, whereas Su 2358 was active only at the highest concentration used (0.05 per cent).

Exp. Bk. 12/19: Influence of delayed therapy with Su 1795, Su 1906, and Su 2079 on guinea pig tuberculosis (table 3).

THIOUREAS TESTED		
	R	R_1
Su 1795	C_2H_5O—	iso-C_4H_9O—
Su 1906	n-C_4H_9O—	$N(CH_3)_2$—
Su 2079	n-C_4H_9O—	$(C_2H_5)_2NCH_2CH_2O$—

Treatment begun: sixtieth day post infection.
Duration of treatment: 100 days.

Influence of delayed therapy: It is evident from the results presented in table 3 that, in spite of delaying treatment for sixty days, Su 1795 (0.1 per cent) demonstrated strong antituberculous activity which approximately equaled that of isoniazid, as determined by macroscopic and microscopic examinations. Both

TABLE 3

INFLUENCE OF DELAYED THERAPY WITH SU 1795, SU 1906, AND SU 2079 ON GUINEA PIG TUBERCULOSIS

COMPOUND	PER CENT OF CONCENTRATION IN DIET	NUMBER OF ANIMALS	AVERAGE MACROSCOPIC INVOLVEMENT					AVERAGE MICROSCOPIC INVOLVEMENT			
			Spleen	Lungs	Liver	Site of Inoculation	Total Involvement	Spleen	Lungs	Liver	Total Involvement
Su 1795	0.1	17	1.8	6.5	8.8	1.2	18.3	0	0	1.1	1.1
Su 1906	0.1	18	10.3	12.2	9.0	3.9	35.4	Not Evaluated			
Su 2079	0.1	17	6.5	7.0	7.6	6.0	27.1	Not Evaluated			
Isoniazid	0.1	18	2.8	5.0	6.1	1.1	15.0	0	0	0	0
Controls	—	17	27.4	21.2	24.1	10.0	82.7	16.3	11.5	21.9	49.7
Pretreatment controls*	—	5	35.0	22.0	24.0	10.0	91.0	20.8	25.0	33.3	79.1

* These animals were sacrificed at the commencement of therapy (sixtieth day post infection).

substances abolished all microscopic evidence of tuberculosis, and only occasional foci of lymphocytes in the lungs and liver were detected which undoubtedly represented healed tubercles. In a few animals, small foci of scarring and calcification were observed in the spleen, probably indicating previous tuberculous inflammatory foci. The amount of tuberculosis in the pretreatment controls was extensive and more marked than that found in the untreated controls. This observation was made by both the microscopic and macroscopic appraisals. The microscopic differentiation between the two control groups was somewhat greater than the macroscopic estimate would indicate and is due to the fact that on gross examination areas of scarring were considered as foci of activity.

Therapeutic Activities of Combinations of Su 1795 with Isoniazid or Streptomycin (table 4)

Treatment started: twenty-seventh day post infection.

Duration of treatment: 70 days.

According to the data shown in table 4, the combination of suboptimal doses of Su 1795 and of isoniazid or streptomycin resulted in considerably enhanced therapeutic effects in guinea pig tuberculosis.

Toxicity Studies in Normal Guinea Pigs Fed with Diets Containing 1 per cent and 2 per cent of Su 1795 (table 5)

Uninfected guinea pigs, weighing approximately 600 gm, were divided into groups of 10 animals each and given, ad libitum, diets containing 1 per cent and 2 per cent of Su 1795. On the sixtieth day, the guinea pigs were sacrificed, and spleens, kidneys, livers, lungs, and hearts were removed. The organs were weighed and also examined histologically for evidence of toxicity.

Microscopic examinations of sections of all of the guinea pig organs gave no evidence of toxic changes in the animals treated with the medicated diets. A

TABLE 4

THERAPEUTIC ACTIVITIES OF COMBINATIONS OF SU 1795 WITH ISONIAZID OR STREPTOMYCIN

TREATMENT	DOSAGE	NUMBER OF ANIMALS	AVERAGE MACROSCOPIC INVOLVEMENT				
			Spleen	Lungs	Liver	Site of Inoculation	Total Involvement
Su 1795	0.005% diet	12	10.0	8.3	16.3	2.5	37.1
Isoniazid	0.005% diet	13	17.3	20.8	19.0	3.1	60.2
Combination of both	As above	14	3.2	5.0	5.7	2.9	16.8
Su 1795	0.025% diet	12	11.6	5.8	14.6	1.7	33.7
Isoniazid	0.005% diet	13	17.3	20.8	19.0	3.1	60.2
Combination of both	As above	12	2.5	5.8	1.7	1.7	11.7
Su 1795	0.005% diet	12	10.0	8.3	16.3	2.5	37.1
Streptomycin	1.0 mg. daily, subcutaneously	11	20.0	11.8	16.4	4.5	52.7
Combination of both	As above	12	3.3	2.5	1.7	1.7	9.2
Su 1795	0.025% diet	12	11.6	5.8	14.6	1.7	33.7
Streptomycin	1.0 mg. daily, subcutaneously	11	20.0	11.8	16.4	4.5	52.7
Combination of both	As above	12	0.8	3.3	1.7	3.3	9.1
Untreated controls (97 days)		11	27.8	23.6	23.6	10.0	85.0
Pretreatment controls (twenty-seventh day)		6	28.3	8.3	18.3	8.3	63.3

TABLE 5

TOXICITY OF 1 PER CENT AND 2 PER CENT SU 1795 IN NORMAL GUINEA PIGS

			CONTROLS (NORMAL DIET)	1 PER CENT SU 1795	2 PER CENT SU 1795
Total body weight (gm.)	At start	Range	462–838	525–710	465–747
		Average	659	606	609
	At end	Range	565–795	553–670	442–747
		Average	694	605	578
	Average change in weight		+35	−1	−31
Organ weights on sixtieth day of feeding (gm.)	Spleen	Range	0.50–1.59	0.6–1.1	0.49–1.1
		Average	1.03	0.8	0.8
	Kidneys	Range	4.9–6.5	4.8–7.0	4.5–7.8
		Average	5.4	5.8	5.9
	Liver	Range	23.0–37.0	28.9–40.0	25.5–36.5
		Average	27.2	35.4	30.8
	Lungs	Range	5.5–9.0	6.0–7.1	5.1–7.8
		Average	6.5	6.3	6.2
	Heart	Range	2.0–4.0	2.0–3.0	2.0–3.9
		Average	2.9	2.3	3.1

minimal degree of fatty metamorphosis of the liver was infrequently observed in the control as well as in the treated groups. Although the degree of infiltration of fat may have been slightly greater in the 1 per cent diet group, the extent of variation between individual animals within each group is greater than the variation observed between groups. Inasmuch as this type of change is of a nutritional character, it is probable that the experimental animals consumed less food as indicated by their weight loss, and thus developed nutritional deficiencies. On the basis of the above findings, it appears that, within the limits of this experiment, Su 1795 is nontoxic for guinea pigs at the concentrations tested.

DISCUSSION

The data presented in this report support the earlier observations made with mice that a number of diphenyl thioureas possess strong antituberculous activity in experimentally infected animals. In both mice and guinea pigs, certain of these compounds had high activities at concentrations in the diet as low as 0.05 per cent. An interesting difference exists, however, between these 2 animals with respect to the chemotherapeutic action of the thiourea derivatives. As reported in an earlier publication, consistent quantitative differences were observed in the mouse between the more active thioureas and isoniazid when compared on the basis of dosage response. Isoniazid was considerably more active than any of the thioureas as measured by survival time (T_{50} values). In the guinea pig, however, this difference in activity barely exists since the activity of certain thioureas in guinea pigs was almost identical to that obtained with isoniazid. It should be emphasized, however, that the methods used in analyzing the effectiveness of thioureas in both animal species differed in that the principal measurement of activity in the mouse was the survival rate, whereas, in the guinea pig experiments, the measure was associated with the extent of disease involvement present at a fixed sacrifice point.

Another important difference between the mouse and guinea pig data pertains to the effects of these antituberculous agents upon the development of pulmonary lesions. Thioureas, such as Su 1795 and Su 1906, at optimal doses, were capable of eliminating all evidence of active tuberculosis in the guinea pig in that microscopic examination revealed no residual evidence of caseation necrosis or proliferative tuberculosis. In mice, on the other hand, these same compounds had but slight retarding effect upon the development of gross and microscopic lesions. Considerable interest has been evoked concerning the significance of these differences in the response by infected mice and guinea pigs to treatment with antituberculous agents. The practical question of how they reflect upon the clinical usefulness with regard to the thioureas has yet to be determined.

The emergence of drug-resistant strains of tubercle bacilli has played a great role in many of the discussions pertaining to the chemotherapy of antituberculous agents. It is a generally accepted fact that the relative ease with which resistant strains emerge after contact with streptomycin or isoniazid, either in the test tube or in the human host, constitutes a serious problem in the treatment of tuberculosis with these substances. With respect to the thioureas, it was found that resistant strains develop *in vitro* with greater difficulty. Indeed, a greater

number of transfers of the organism through broth containing thioureas were necessary before obtaining an appreciable degree of resistance than was the case with streptomycin or isoniazid, although it should be noted that the initial susceptibility of *M. tuberculosis* to the thiourea derivatives is much less than that exhibited toward streptomycin and isoniazid.

Despite a number of attempts to isolate resistant strains from infected mice treated with the various thioureas, none were obtained. This observation may not be too surprising, however, since it is also rare to obtain resistant tubercle bacilli from infected mice treated with either streptomycin or isoniazid.

In vitro cross-resistance studies revealed that strains of H37Rv made resistant to thioureas were highly susceptible to streptomycin, para-aminosalicylic acid, and isoniazid, but exhibited cross-resistance to amithiozone. This indicates that either the thioureas and thiosemicarbazones act by virtue of a common, directly active chemical component or that the biologic attack upon the tubercle bacillus by both classes of compounds is identical.

SUMMARY

Seven of eight 1,3-diphenyl thiourea derivatives, selected on the basis of their antituberculous activities in mice, have been shown to exert suppressive effects on the course of the disease in experimentally infected guinea pigs.

When therapy was delayed for sixty days after infection, Su 1795 (4-ethoxy-4′-isobutoxythiocarbanilide) was capable of virtually abolishing all microscopic evidence of active infection in the treated guinea pigs.

Combinations of suboptimal concentrations of Su 1795 and isoniazid or streptomycin resulted in considerably enhanced therapeutic effects.

Histologic examination of the organs of normal guinea pigs fed for sixty days with a diet containing 2.0 per cent of Su 1795 failed to demonstrate evidence of toxicity.

SUMARIO

Actividad Antituberculosa de las Tioureas Substituídas: III. Actividad en los Cobayos

Siete de ocho derivados de la 1,3-difenil-tiourea, escogidos a base de su actividad antituberculosa en los ratones, ejercieron, según se observó, efectos supresores sobre la evolución de la dolencia en cobayos infectados experimentalmente.

Cuando se demoró la terapéutica hasta sesenta días después de la infección, el Su 1795 (4-etioxi-4-isobutoxitiocarbanilida) se mostró capaz de abolir virtualmente todo signo microscópico de infección activa en los cobayos tratados.

Las combinaciones de concentraciones subóptimas de Su 1795 y de isoniacida o estreptomicina dieron por resultado efectos terapéuticos considerablemente mayores.

El examen histológico de los órganos de cobayos normales alimentados durante sesenta días con un régimen dietético que contenía 2.0 por ciento de Su 1795 no reveló signos de toxicidad.

RESUME

Activité antituberculeuse des thio-urées substituées: III. Activité chez le cobaye

Parmi huit dérivés 1,3-diphényl thio-urée, dont la sélection était fondée sur leur pouvoir antituberculeux chez la souris, sept ont fait preuve d'une action suppressive sur le cours de l'affection chez le cobaye tuberculisé.

Après un délai de soixante jours à la suite de l'inoculation, le traitement par le Su 1795 (4-éthyoxy-4-isobutoxythiocarbanilide) était capable de supprimer virtuellement tout signe histo-pathologique d'infection chez les cobayes traités.

Les associations de concentrations sous-optima de Su 1795 et d'isoniazide ou de streptomycine ont produit un renforcement de l'action thérapeutique.

L'examen histologique des organes de cobayes soumis pendant soixante jours à un régime contenant 2 pour cent de Su 1795 n'a révélé aucun signe de toxicité.

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THE APPLICATION OF THE MIDDLEBROOK-DUBOS HEMAGGLUTINATION TEST IN TUBERCULOSIS OF CHILDREN[1]

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INTRODUCTION

The differentiation between activity and inactivity in tuberculosis is a difficult problem. A step forward toward its solution has been achieved with the application of the Middlebrook and Dubos hemagglutination test. In fact, most of the data accumulated in the literature suggest that this test has considerable value. Nevertheless, it remains to be proved that the test is specific for tuberculosis. Most of the compiled data are in favor of its specificity but not all of the data for positive reactions have been observed in a 1:8 dilution in healthy subjects. Smith and Scott (1) found 3 per cent of positive results among healthy subjects with a negative tuberculin reaction. It has also not been shown that the test can differentiate activity from inactivity in tuberculosis.

Almost all writers agree that positive hemagglutination reaction in a 1:2 dilution does not imply activity of a tuberculous process because the serum of patients with old, treated tuberculosis may give a positive reaction in this dilution.

Peterson and associates (2) believe that the hemagglutination reaction is of little value both in following the evolution of a tuberculous process and in the differential diagnosis between activity and inactivity in a particular infection. Smith and Scott (1) had noted a fall in titer or a reversal of the reaction in chronic forms of tuberculosis and in instances of the disease with a severe prognosis. In the first instance, these writers suggest that the hemagglutinins are lacking because there is not enough antigenic stimulation from the cured tuberculous lesion. In the latter instance, it is suggested that the antibodies are neutralized by substances released from the rapidly growing bacteria. Kirby and co-workers (3), Peterson and his associates (2), Sohier and Termberger (4), and Lugentini and Boisvert (5) share the same views.

The present study has been designed in an attempt to answer some of the above questions. The Middlebrook and Dubos hemagglutination test has been investigated in 340 patients treated at the Children's Clinic of Athens University.

MATERIALS AND METHODS

Hemagglutination technique: The Smith and Scott modification of the Middlebrook-Dubos technique was used in the present study.

Material: Two hundred and twenty-nine patients with tuberculosis and 111 control subjects (healthy persons with negative tuberculin reactions) have been examined with

[1] From the Pediatric Clinic of Athens University, Athens, Greece.

the Middlebrook and Dubos hemagglutination test. The 229 tuberculous patients had the following disease:

25 patients with positive tuberculin reaction without clinical symptoms
42 patients vaccinated with BCG
162 patients with tuberculosis of various types, i.e.,
6 with miliary tuberculosis
90 with tuberculous meningitis
5 with tuberculosis of the mediastinal lymph nodes
15 with pleurisy
2 with osteoarthritis
2 with erythema nodosum
30 with primary complex
12 with subsiding adenitis

As may be seen in table 1, in the 111 nontuberculous patients, the serum hemagglutination reaction as a rule was negative. Indeed, the reaction was positive in only 2 patients and then only in a 1:2 and 1:4 dilution, respectively.

Of 25 patients with positive tuberculin reactions, but no other evidence of disease, the hemagglutination reaction was positive in 15. The reaction was positive in a 1:2 dilution in 2 patients, and in a 1:4 dilution in 4 patients. In the remaining 10 patients, the hemagglutination reaction was negative.

Of 42 BCG-vaccinated persons, the hemagglutination reaction was positive in 31 and negative in 11.

Finally, in 162 tuberculous subjects, the hemagglutination reaction was positive in 158 (97.5+ per cent) and negative in the remaining 4 (2.4 per cent). The dilution titers and the percentage proportion of the positive reactions in the various forms of tuberculosis may be seen in table 1.

Comment: It is obvious from the above data that the hemagglutination reaction is the one of choice in tuberculous infections. The fact that the lowest percentage of negative reactions occurred in tuberculous patients (2.4 per cent) supports fully the above viewpoint.

The fact that, in a total of 450 tests applied in the beginning, as well as during the course of the 90 cases of tuberculous meningitis, no negative reaction was encountered is in agreement with this viewpoint. The reversal of the reaction to negative observed in 15 cases occurred either in patients who had shown recovery by clinical and laboratory criteria or in patients whose state worsened considerably.

Could the hemagglutination reaction in general and, more specifically, the titer of the hemagglutination serve as a criterion in the differential diagnosis of an active infection from an inactive one, or from a clinically cured tuberculous infection?

This question is obviously the most interesting, and the specific value of the method has been based on its use in the differential diagnosis between active and inactive cases.

The conclusions drawn from the results obtained in the various forms of tuberculous infection and, more specifically, during the course of tuberculous meningitis, as they appear in the tables and figures, permit a somewhat limited affirmative answer. The present writers believe that the activity of tubercle bacilli is re-

TABLE 1

HEMAGGLUTINATION REACTION IN TUBERCULOUS AND NONTUBERCULOUS SUBJECTS

PATIENTS EXAMINED	TOTAL NUMBER OF PATIENTS	NUMBER OF PATIENTS (PER CENT)								ABOVE 1:8 DILUTION	BELOW 1:8 DILUTION
		DILUTION									
		—	1:2	1:4	1:8	1:16	1:32	1:64	1:128		
										per cent	*per cent*
Nontuberculous subjects	111	109 (98.2)	1 (0.90)	1 (0.90)						0	100
Positive tuberculin reaction only	25	10 (40)	11 (44)	4 (16)						0	100
BCG-vaccinated	42	11 (26.19)	9 (21.42)	10 (23.80)	5 (11.90)	6 (14.31)	1 (2.38)			28.59	71.41
Active tuberculosis	162	4 (2.46)	11 (6.78)	38 (23.40)	52 (32.09)	37 (22.83)	17 (10.59)	2 (1.23)	1 (0.62)	67.36	32.64
Subsiding primary complex	12	2 (16.62)	4 (33.33)	5 (41.66)	1 (8.39)					8.39	91.61
Primary complex with fever	30	2 (6.66)	1 (3.33)	11 (36.73)	12 (39.96)	4 (13.32)				53.28	46.72
Pleurisy	15	0-0	0-0	5 (33.33)	6 (40)	3 (20)	1 (6.67)			66.67	33.33
Erythema nodosum	2			1 (50)			1 (50)			50	50
Mediastinal lymphadenopathy	5			1 (20)	1 (20)	3 (60)				80	20
Osteoarthritis	2						2 (100)			100	0
Miliary tuberculosis	6			1 (16.6)		3 (50.2)	2 (33.2)			83.4	16.6
Tuberculous meningitis at its peak	(90)		(1)	(13)	(35)	(26)	(12)	(2)	(1)		
Number of tests	256*		3 (1.20)	32 (12.5)	100 (39.06)	78 (30.46)	30 (11.71)	10 (3.90)	3 (1.17)	86.30	13.70
	340										

Number of patients and their percentage proportions in the various dilutions.

* In the cases of tuberculous meningitis, the number of reactions is also recorded.

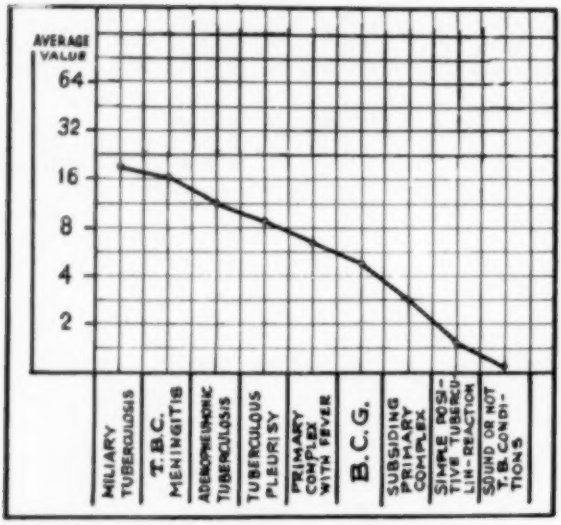

FIG. 1. Agglutination titer: *(1)* in patients with tuberculosis; *(2)* in patients who have recovered from tuberculosis; *(3)* in nontuberculous subjects.

flected, to a certain extent, in an increase of the hemagglutination titer. Moreover, the facts that, in patients with only a positive tuberculin reaction, the percentage proportion of negative titers appears considerable (40 per cent) and that there is a relative increase of the negative titers in fully recovered tuberculous meningitis patients are in support of this viewpoint.

Average value of hemagglutination reaction related to severity of tuberculosis: In figure 1, the average value of the hemagglutination titer[2] is related to the severity of the tuberculous infection and, as may be seen, the correspondence is close. Thus, the highest hemagglutination titer (corresponding to 1:16 dilution or more, or to an average value of 19.33) was found in miliary tuberculosis; whereas the lowest titer (corresponding to 1:2 dilution or lower and to an average value of 1.6) was observed in persons whose sole evidence of infection was a positive tuberculin reaction.

Next in order to miliary tuberculosis comes tuberculous meningitis. The latter shows at its peak an average value of 16.26, whereas the percentage proportion of the titer dilutions above 1:8 comes to 86.3 per cent. The hemagglutination titer has been found to be high in the presence of mediastinal lymphadenitis, with an average hemagglutination titer value of 12 and a dilution percentage proportion of more than 1:8 of 80 per cent. In pleurisy, the average hemagglutination

[2] The average value of the hemagglutination titer in a given group of sera is the sum of agglutinating units divided by the number of specimens. The agglutinating unit is the amount of antibody required to produce a positive reaction in this test, i.e., when a serum has an agglutinating titer of 1:64, it contains 64 units (6).

titer value was 9.2 and the percentage proportion of patients with a titer above 1:8 dilution, 66.67 per cent.

A definite difference was found between clinically evident adenitis, with an average hemagglutination titer of 6.83 (and a percentage proportion with a titer above 1:8 dilution of 53.28 per cent), as compared to the subsiding forms of the disease. In the latter, the percentage proportion titer above 1:8 was 8.39, whereas the hemagglutination titer average value was 3.

No hemagglutination titer above 1:8 dilution was found in persons whose sole evidence of tuberculosis was a positive tuberculin reaction. The explanation of this phenomenon might be that in this phase of the disease a decrease of antibodies occurs, probably because there is no considerable antigenic stimulation on the part of the tuberculous lesions.

A fall and reappearance of the hemagglutination reaction (6 cases) has been observed in very severe infections and even immediately before death. The present writers agree with Scott and Smith (1) that, in these cases, the antibodies are presumably eliminated by factors produced by the fast-growing bacteria.

Behavior of reaction at various stages of meningitis: It has been possible in the meningitis cases to consider more specifically the behavior of the hemagglutination reaction at various stages of the disease because of the greater length of time the patients with meningitis remain in the Clinic. The conclusions drawn are in support of the viewpoint that the hemagglutination titer is influenced by the course of the disease. The test has been repeated throughout the course of the first eight months of the disease, during which period 450 tests were made. In 65 instances, the reaction was repeatedly studied until the patients were discharged from the hospital; in 15 patients the titer was again determined at some time after discharge.

The results are recorded in tables 2 and 3 and are illustrated in figures 2, 3, 4, and 5. The hemagglutination titer percentage proportions of all tuberculous meningitis patients are illustrated in table 5. In figure 2 is shown the dilution titer percentage proportion of the above 1:8 dilutions and of those below 1:4 in

TABLE 2

PERCENTAGE PROPORTION OF DILUTION TITER DURING THE VARIOUS PHASES OF TUBERCULOUS MENINGITIS

Dilutions	(—)	1:2	1:4	1:8	1:16	1:32	1:64	1:128	
PHASE OF DISEASE	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	Number of Reactions (Per Cent)	TOTAL REACTIONS
Onset of disease	0 (0)	9 (9.18)	22 (22.44)	27 (27.55)	26 (26.53)	11 (11.22)	3 (3.18)		98
Peak of disease		3 (1.18)	32 (12.50)	100 (39.06)	78 (30.46)	30 (11.72)	10 (3.90)	3 (1.18)	256
Recovery	17 (25.38)	14 (20.89)	16 (23.88)	16 (23.88)	4 (5.97)				67
Check of titer after recovery	10	5							15
Worsening	4 (28.57)	2 (14.29)	6 (42.85)	2 (14.29)					14
									450

TABLE 3

PERCENTAGE PROPORTION OF THE DILUTION TITERS

(Above the 1:8 Dilutions and Below the 1:4 Dilutions in the Various Phases of Tuberculous Meningitis in 90 Cases—Total of Tests, 450)

PHASES OF DISEASE	ABOVE THE DILUTION 1:8	BELOW THE DILUTION 1:4
	per cent	*per cent*
Onset of disease	68.48	31.52
Peak of the disease	86.32	13.68
Recovery	29.85	70.15
Check of titer 1–2 months after recovery	0	100
Worsening	14.29	85.71

14 patients with tuberculous meningitis with fortnightly determinations and which had a four months' course. The variation of the average value for the hemagglutination titer in the same patients studied fortnightly is given in figure 4. In figure 5, the most representative curves of the course of the hemagglutination reaction throughout the disease are illustrated.

The cerebrospinal fluid of 30 patients with tuberculous meningitis was also studied, and it was not possible to demonstrate the presence of hemagglutination antibodies in any of the fluids.

As may be seen in the figures and tables, at the onset of the disease a dilution titer higher than 1:8 was present in 68 per cent of the patients and the average titer value was 13.34. During the course of the disease, the percentage of high titers increased to 86.3, with an average titer value of 16.26. Finally, during the period of recovery, as judged by clinical and laboratory criteria, the percentage of patients with titers above 1:8 fell considerably to 29.85, with a 4.22 average titer value.

As a rule, the titer proved low in these patients who were discharged from the Clinic after recovery and later were readmitted for follow-up observations. In these, the percentage with titers above 1:8 was zero, with 0.8 average titer value. Repeated determinations of the hemagglutination is of importance in the very grave forms of the disease. In only 2 of the 10 seriously ill patients whose serum was examined was there a titer above the 1:8 dilution.

Comment: The behavior of the hemagglutination reaction during the course of tuberculous meningitis was in further support of the conclusion stated above, that a considerable connection exists between the hemagglutination titer and the degree of activity of the tuberculous infection.

From a comparison made of the positive reactions which were obtained in the present study and the clinical and other observations on the patients, it appears that positive reactions in titers of 1:2 and 1:4 do not support the diagnosis of active tuberculosis since they also appear in patients with simple positive tuberculin reaction. Likewise, patients with titers above 1:8 can be considered to have an active tuberculous process. In fact, a positive hemagglutination test with a titer above 1:8 was found principally in active tuberculous infection. In such cases, the percentage with only a 1:4 titer was relatively small.

Only 53 of 162 patients with active tuberculosis showed a hemagglutination

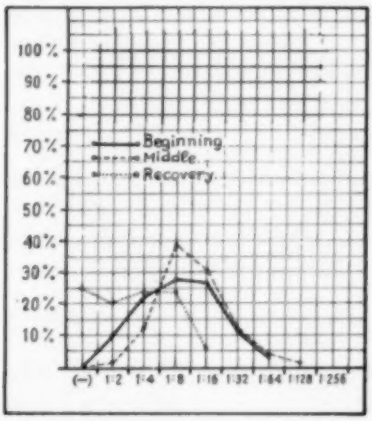

FIG. 2. Percentage of dilution titers during the different phases of tuberculous meningitis.

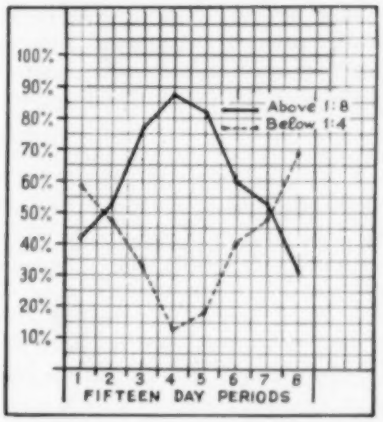

FIG. 3. Percentage of dilution titers: (*1*) above 1:8; (*2*) below 1:4, at fifteen-day intervals in 17 cases of tuberculous meningitis.

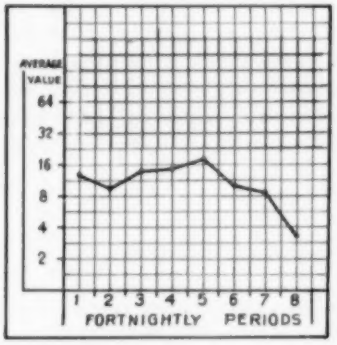

FIG. 4. Variation of agglutination titer at fortnightly intervals in 17 patients with tuberculous meningitis who recovered in four months.

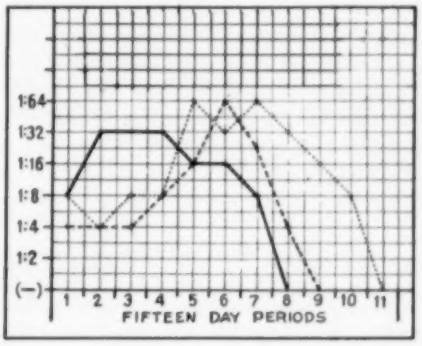

FIG. 5. Curves showing agglutination titers at fifteen-day intervals in 3 cases of tuberculous meningitis.

titer below 1:8 and these were chiefly instances of primary complex or subsiding adenitis. Of 354 tests made during the course of tuberculous meningitis before recovery, only 66 (18.64 per cent) gave a hemagglutination titer below the 1:8 dilution.

A high dilution titer in patients with a history of treated tuberculosis was found only when the recovery was recent. The lowering of the titer runs parallel to the course of the disease. This became clear during the follow-up of the patients with tuberculous meningitis who had a high titer during the immediate period of recovery and a lower titer in the months thereafter.

After recovery from tuberculous meningitis, while the tuberculin reaction remained positive, the hemagglutination reaction fell in titer or disappeared altogether. It is believed that this phenomenon may be explained by a difference in the mechanism of the two reactions.

SUMMARY

The hemagglutination reaction test is specific for tuberculosis and therefore constitutes a useful tool in the diagnosis of the disease. The hemagglutination reaction is positive in higher titer when the tuberculous process is active, so the test may, with certain limitations, serve as a proof of the seriousness of the disease.

In the present study, the highest hemagglutination titers were obtained in miliary tuberculosis and the next highest occurred in tuberculous meningitis. In other forms of tuberculosis, the height of the titer appeared to depend on the severity of the disease. The titer was low during recovery, as judged by clinical or laboratory criteria, and was likewise low during periods shortly before death.

The present writers observed a somewhat parallel course between the hemagglutination reaction and the tuberculin reaction. When comparing the course of the tuberculin reaction with that of the hemagglutination reaction, the former (already high at the beginning of the disease) increased still more with the improvement of the patient's condition and remained high until recovery. On the contrary, the hemagglutination reaction, rather low at the beginning of the disease, increased gradually until it reached a peak in the middle of the disease and then gradually decreased and sometimes disappeared completely when recovery occurred. It is only in very severe cases that both the tuberculin and the hemagglutination reactions behave in the same way, that is to say, they both decrease or disappear.

SUMARIO

La Aplicación de la Prueba de Hemaglutinación de Middlebrook-Dubos en la Tuberculosis de los Niños

La reacción de hemaglutinación de Middlebrook-Dubos es específica para la tuberculosis y constituye, por lo tanto, un instrumento útil en el diagnóstico de la enfermedad.

Dicha reacción parece ser más intensa en la tuberculosis activa, de modo que, con ciertas limitaciones, puede servir de prueba de la gravedad de la dolencia.

El título más alto de hemaglutinación corresponde a la granulia, viniendo después la meningitis tuberculosa. En otras formas de tuberculosis, la magnitud del título depende de la gravedad de la afección.

El título es bajo durante la reposición clínica o de laboratorio así como durante los períodos de agravación de la dolencia.

La hemaglutinación y la reacción a la tuberculina mostraron una evolución algo paralela. Al compararlas, la primera, ya alta en la iniciación de la enfermedad, sube todavía más al mejorar el estado del enfermo y permanece alta hasta la curación. Por el contrario, la segunda, algo baja en la iniciación de la enfermedad, sube gradualmente hasta llegar a una cumbre a mediados de la enfermedad, bajando después gradualmente y a veces desapareciendo del todo cuando ocurre la curación. Sólo en los casos muy graves es que tanto la reacción a la tuberculina como el título de la hemaglutinación se comportan del mismo modo, es decir, que ambos disminuyen o desaparecen.

RESUME

L'application du test d'hémagglutination de Middlebrook-Dubos dans la tuberculose de l'enfant

Le test d'hémagglutination de Middlebrook-Dubos est spécifique pour la tuberculose, en conséquence, il constitue un instrument utile dans le diagnostic de cette affection.

La réaction d'hémagglutination est plus accentuée dans la tuberculose en activité, aussi, compte tenu de certaines limitations, elle permet d'apprécier la gravité de la maladie.

Le titre d'hémagglutination le plus élevé s'obtient dans la miliaire et le titre immédiatement au-dessous dans la méningite tuberculeuse. Dans les autres formes de la tuberculose, l'importance du titre d'hémagglutination dépend de la sévérité de l'affection.

Le titre est faible pendant les périodes où la guérison se manifeste tant cliniquement que par les résultats des examens de laboratoire; il en est de même pendant les périodes d'aggravation de la maladie.

Les auteurs ont observé un certain parallélisme entre l'hémagglutination et la réaction à la tuberculine. Quand on compare l'évolution de la réaction à la tuberculine à celle de l'hémagglutination, la première, déjà forte au début de la maladie, augmente encore avec l'amélioration de l'état du malade et son degré demeure élevé jusqu'à la guérison. Au contraire, la seconde réaction, qui est plutôt faible au début de l'affection, augmente graduellement, atteint un sommet pendant la phase moyenne de l'évolution et décroît progressivement pour disparaître parfois complètement quand la guérison survient. Ce n'est que dans les cas très sévères que la réaction à la tuberculine et l'hémagglutination se comportent de la même manière, c'est à dire que toutes deux décroissent ou disparaissent.

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URINE CULTURES FOR M. TUBERCULOSIS DURING CHEMOTHERAPY[1]

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INTRODUCTION

M. tuberculosis is difficult to culture from urine specimens even under favorable conditions. Delays in the diagnosis of renal tuberculosis sometimes result from this fact, with serious consequences to the patient. If the methods for culturing tubercle bacilli from the urine become even less sensitive once chemotherapy is started, "false negative" results might create the impression that the renal infection had been arrested and lead to premature cessation of treatment. Accurate knowledge of the bacteriologic status of the patient is especially important in genitourinary tuberculosis since urological foci can discharge tubercle bacilli into the urine for years without causing any symptoms (1). Indeed, approximately one-half of the patients seen by the writers had no urinary symptoms despite the presence of active genitourinary lesions.

In routine medical practice, urine cultures are obtained only at long intervals, making it difficult to define the accuracy of the methods for culturing *M. tuberculosis* from urine. In contrast, at the Research Unit for Genito-Urinary Tuberculosis, the routine procedure is to culture three 24-hour urine specimens from every patient every two weeks on media appropriate for tubercle bacilli. During 1952, the total number of urine specimens examined was 1,564, and the total number of specimens cultured for *M. tuberculosis* was 4,692, thus providing an excellent opportunity to study the reliability of cultures under various conditions.

During the past few years it seemed that the recovery of *M. tuberculosis* from the urines of patients receiving chemotherapy was not as high as could be anticipated from the clinical appearance of the lesions. A survey of a large number of cultures also gave the impression that there was an immediate drop in the numbers of cultures positive for tubercle bacilli just after therapy was started. A similar impression that during treatment there was a decrease in positive cultures and guinea pig inoculations has been stated by Ljunggren (2).

It seemed important, therefore, to investigate the influence of the administration of antituberculous drugs upon the excretion of culturable tubercle bacilli in the urine. The present report is based on a study of 1,194 urine cultures from 6 men with renal tuberculosis before, during, and immediately after chemotherapy. Five of the 6 patients received isoniazid and the other patient received isoniazid, streptomycin, and para-aminosalicylic acid (PAS). The total duration of treatment for each patient was twelve months.

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MATERIALS AND METHODS

All urine specimens represented 24-hour collections voided directly into sterile flasks without the use of any chemical preservative. Three consecutive specimens were collected every two weeks, except when therapy was interrupted, during which times 24-hour urine specimens were collected daily. The specimens were flocculated with 1 to 2 cc. of 23 per cent solution of trisodium phosphate for every 100 ml. of urine, and sedimented overnight in a slanted position. An equal volume of 23 per cent trisodium phosphate was added to the sediment, and the mixture was shaken and digested for sixteen hours at 37°C. It was next centrifuged, and the sediment was neutralized to pH 6.8. The concentrate was then cultured on three tubes, one of Löwenstein-Jensen (3), one of Petragnani (4), and one of American Trudeau Society (5) medium. The cultures were observed for eight weeks before being discarded as sterile.

RESULTS

Three hundred and ninety-eight specimens of urine, representing a total of 1,194 cultures, were studied. Among the 398 cultured specimens, 149 were collected when the patients were receiving no antimicrobial therapy, and 249 were collected while the patients were receiving such therapy. Of the 149 specimens collected when no chemotherapy was being given, 49 (42.9 per cent) were positive for *M. tuberculosis*. This total of 149 specimens represented specimens obtained both before and after therapy. A subdivision of this total into two groups (table 2) showed that, of 93 specimens collected before antimicrobial therapy, 38 (40.9 per cent) were positive for *M. tuberculosis*. Among 56 specimens collected after drug treatment was stopped, only 11 (19.6 per cent) were similarly positive.

In contrast to these findings, of 249 specimens (representing 747 cultures) collected during drug therapy, only 7 (2.8 per cent) were positive for *M. tuberculosis* (figure 1, table 1). All of these positive cultures (2.8 per cent) were obtained from the same patient. This low percentage of recoveries became even

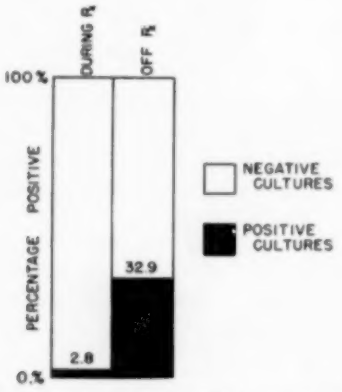

FIG. 1. Urine cultures for *M. tuberculosis*. Urine cultures collected during treatment were rarely positive. Three hundred and ninety-eight specimens obtained from 6 patients with renal tuberculosis were studied.

TABLE 1

URINE CULTURES FOR M. TUBERCULOSIS OBTAINED DURING TREATMENT COMPARED WITH CULTURES OBTAINED IN THE ABSENCE OF TREATMENT

NUMBER	GRAND TOTAL SPECIMENS	NOT DURING TREATMENT			DURING TREATMENT		
		Total Specimens	Positive	Negative	Total Specimens	Positive	Negative
1	44	15	1 (6.6%)	14 (93.4%)	29	0 (0.0%)	29 (100.0%)
2	87	28	8 (28.6%)	20 (71.4%)	59	0 (0.0%)	59 (100.0%)
3	74	25	7 (28.0%)	18 (72.0%)	49	0 (0.0%)	49 (100.0%)
4	57	20	9 (45.0%)	11 (55.0%)	37	0 (0.0%)	37 (100.0%)
5	47	37	10 (27.0%)	27 (73.0%)	10	0 (0.0%)	10 (100.0%)
6	89	24	14 (58.4%)	10 (41.6%)	65	7 (10.8%)	58 (89.2%)
Totals	398	149	**49 (32.9%)**	100 (67.1%)	249	**7 (2.8%)**	242 (97.2%)

A total of 49 specimens (32.9 per cent) were positive for *M. tuberculosis* while the patients were not on treatment in contrast to only 7 specimens (2.8 per cent) which were similarly positive during treatment. All seven positive cultures were obtained from the same patient.

TABLE 2

URINE CULTURES FOR M. TUBERCULOSIS OBTAINED WHILE PATIENTS WERE RECEIVING NO CHEMOTHERAPY

NUMBER	GRAND TOTAL OF SPECIMENS WHILE OFF TREATMENT	BEFORE TREATMENT			AFTER TREATMENT		
		Total Specimens	Positive	Negative	Total Specimens	Positive	Negative
1	15	7	1 (14.3%)	6 (85.7%)	8	0 (0.0%)	8 (100.0%)
2	28	10	8 (80.0%)	2 (20.0%)	18	0 (0.0%)	18 (100.0%)
3	25	19	7 (36.8%)	12 (63.2%)	6	0 (0.0%)	6 (100.0%)
4	20	17	9 (53.0%)	8 (47.0%)	3	0 (0.0%)	3 (100.0%)
5	37	31	8 (25.8%)	23 (74.2%)	6	2 (33.3%)	4 (66.7%)
6	24	9	5 (55.6%)	4 (44.4%)	15	9 (60.0%)	6 (40.0%)
Totals	149	93	**38 (40.9%)**	55 (59.1%)	56	**11 (19.6%)**	45 (80.4%)

A total of 38 specimens (40.9 per cent) were positive for *M. tuberculosis* before treatment, while only 11 (19.6 per cent) were similarly positive after treatment was terminated. Four of the 6 patients have had no positive cultures in the six months since treatment was terminated.

more significant when the individual charts of the 6 patients were analyzed. All of the 6 patients had excreted culturable tubercle bacilli at some time before drug treatment was started. In 3 of the 6 patients, cultures positive for tubercle bacilli had been obtained as recently as one week before chemotherapy was started. In 5 of the 6 patients, cultures of the urine negative for tubercle bacilli were obtained a few days after chemotherapy was started. The urine of the sixth patient was not cultured until several days later, at which time it too was negative for *M. tuberculosis*.

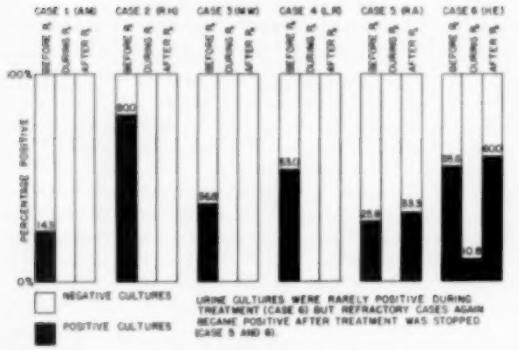

FIG. 2. Urine cultures for *M. tuberculosis* from 6 patients with renal tuberculosis before, during, and after isoniazid treatment.

The percentage of "positive" cultures before, during, and after treatment is presented for each patient in figure 2, in three columns. This figure shows that, with the first 4 patients, cultures positive for tubercle bacilli were obtained only before treatment. The results were different with patients Nos. 5 and 6. Patient No. 5, whose urine cultures were positive for *M. tuberculosis* in 28.8 per cent of the examinations made before therapy, excreted no culturable bacilli during therapy. Once drug therapy was stopped, his urine was again positive for tubercle bacilli in 33.3 per cent of the cultures obtained. Patient No. 6, from whom cultures positive for tubercle bacilli were obtained in 55.6 per cent of the urine specimens studied before drug therapy, had 10.8 per cent "positive" urine cultures during treatment. After drug treatment was stopped, 60 per cent of this patient's urine specimens which were cultured for tubercle bacilli were positive. In patient No. 5, the "positive" cultures of the post-treatment period were obtained on specimens collected on the fifth and seventh days after cessation of therapy. In patient No. 6, the specimens were found to be positive for tubercle bacilli in cultures obtained on the second, third, fourth, sixth, seventh, eighth, tenth, eleventh, and twelfth days after treatment was stopped.

COMMENT

The study of 93 specimens collected before treatment from known tuberculous patients (representing 189 cultures) confirmed the fact that, at best, *M. tuberculosis* is difficult to isolate from the urine. Only 40.9 per cent of the urine cultures from 6 patients with known renal tuberculosis were positive for *M. tuberculosis* under favorable conditions. When tubercle bacilli were isolated before drug treatment, the majority of the strains showed a relatively heavy growth, thus suggesting intermittent excretion of the bacilli by the patients rather than faulty laboratory technique.

The consistent results obtained during the "off-treatment" periods seemed to emphasize the considerably lessened sensitivity of the cultural method when the

patients were receiving isoniazid therapy. As a matter of fact, only 2.8 per cent of the 249 specimens obtained during treatment (747 cultures) were positive for tubercle bacilli.

As "positive" cultures were obtained only before treatment in the first 4 patients, the explanation of the sterile cultures throughout the entire treatment period might have been due to a rapid arrest of the tuberculous process rather than to the presence of drugs in the urine. This is unlikely, since many months of chemotherapy are usually necessary to result in arrest of renal tuberculosis. It seems more likely, therefore, that the "negative" cultures resulted either from temporary influences of the drug on bacilli in the lesion or the actual presence of the drug in the urine.

A different pattern was observed in patients Nos. 5 and 6. In both patients there was a common feature, namely, that the organisms could be recovered with ease shortly after therapy had been stopped. The difference in the patterns of these 2 patients lay in the fact that 10.8 per cent of the specimens cultured during therapy from patient No. 6 were positive for tubercle bacilli. The clinical picture in this patient was one of severe renal and prostatic infection, with a heavy bacilluria which was reflected in more than 50 per cent of "positive" cultures before and after treatment. These facts could have accounted for the occasional "positive" cultures obtained during the treatment. Even in this case, however, as many as 22 successive "negative" cultures were obtained between two "positive" cultures, so that, with a less intensive and prolonged study, the cultures positive for tubercle bacilli might have been missed.

SUMMARY

One thousand one hundred and ninety-four urine cultures for *M. tuberculosis* were obtained before, during, and after one year of isoniazid treatment on 6 patients with bacteriologically proved urinary tuberculosis. Of the specimens obtained before treatment, 40.9 per cent were positive for *M. tuberculosis* on culture but, during treatment, only 2.8 per cent of the urine specimens were similarly positive. After treatment was terminated, culturable tubercle bacilli reappeared in the urine of 2 patients, with the percentage of positive cultures rising to pretreatment levels within ten days after the suspension of treatment.

The present study indicates that there is danger in relying on urine cultures collected during isoniazid therapy in the sense that sterile urine cultures during therapy do not necessarily reflect permanent arrest of the renal tuberculosis. It appears that a waiting period of ten days after the cessation of therapy is necessary before urine cultures are reliable in determining the true bacteriologic status of patients with urogenital tuberculosis.

SUMARIO

Inconstancia de los Urocultivos para el M. Tuberculosis Durante la Quimioterapia

En 6 enfermos que tenían tuberculosis urinaria bacteriológicamente positiva, obtuviéronse mil ciento noventa y cuatro urocultivos en busca del *M. tuberculosis* antes, durante, y después de, un año de isoniacidoterapia.

Un 40.9 por ciento de los cultivos para *M. tuberculosis* fueron obtenidos antes del tratamiento; durante el tratamiento, sólo 2.8 por ciento de los ejemplares urinarios fueron "positivos"; después de terminar el tratamiento, 2 enfermos "reviraron" a positivos, elevándose el porcentaje de cultivos positivos a las cifras anteriores al tratamiento en término de diez días a partir de la suspensión del tratamiento.

Este estudio parece indicar que es peligroso atenerse a los urocultivos recogidos durante el tratamiento con isoniacida, es decir, que los cultivos urinarios negativos para *M. tuberculosis* durante la terapéutica no denotan forzosamente que los enfermos estén curados. Parece que se necesita un período de espera de diez días después de terminar el tratamiento antes de que los urocultivos se vuelvan de nuevo fidedignos para determinar el verdadero estado bacteriológico de los sujetos que tienen tuberculosis urogenital.

RESUME

Les cultures de l'urine pour la recherche du M. tuberculosis ne sont pas valables durant la chimiothérapie

Onze cent quatre-vingt-quatorze cultures d'urine pour l'isolement du *M. tuberculosis* ont été obtenues avant traitement, au cours du traitement et après un an de traitement par l'isoniazide, chez 6 malades atteints de tuberculose des voies urinaires bactériologiquement positive.

Avant le traitement, les cultures positives pour *M. tuberculosis* atteignaient 40, 9 pour cent; au cours du traitement, les prélèvements d'urine ont donné un pourcentage de cultures positives de 2, 8 pour cent seulement; après la fin du traitement, les cultures sont redevenues positives dans 2 cas. Le pourcentage de cultures positives pour le *M. tuberculosis* a repris sa valeur antérieure au traitement dans les dix jours qui ont suivi l'arrêt du traitement.

Cette étude paraît indiquer qu'il y a danger à faire confiance aux cultures d'urine prélevée au cours de l'isoniazide—thérapie, c'est à dire que les cultures négatives pour le *M. tuberculosis* au cours de cette thérapie n'indiquent pas nécessairement la guérison du malade. Il a été observé qu'un délai de dix jours après la cessation du traitement était nécessaire avant qu'on puisse déterminer valablement dans les cultures d'urine le véritable état bactériologique des patients atteints de tuberculose génito-urinaire.

Acknowledgments

The writers wish to express their deepest appreciation for the help of Miss Alfreda Jastremski and Miss Lydia R. Sechler from the Research Unit for Genito-Urinary Tuberculosis; Mr. Alfred Levine from Microbiology Section, Laboratory Service; and Mr. David Lubin, Mr. Paul Newman, and Mr. John Hession from the Medical Illustration Laboratory of the Veterans Hospital, Bronx 68, New York City.

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Case Reports

CYSTIC THYMOMA—THE POSSIBILITY OF CONFUSION WITH TUBERCULOMA[1,2]

GUSTAF E. LINDSKOG

(Received for publication January 15, 1954)

INTRODUCTION

Tumors of the thymus deserve particular study and present-day attention because the organ involved is still on the borderline of medical knowledge. Its basic functions are unknown, and its histogenesis imperfectly understood. The neoplasms arising from the thymus are sufficiently uncommon so that only rarely does a single pathologist and clinical group have direct experience enough to become well versed in their manifestations.

In a group of various mediastinal tumors recently collected by the writer and representing the completely reported case experience of five surgical clinics including (1, 2, 4, 6) his own, there were 22 cases of reputed thymic tumor among 356 primary neoplasms, an incidence of 6.2 per cent. In a fifteen-year experience on the chest service of the Grace-New Haven Hospital there have been 7 surgically removed mediastinal tumors diagnosed as probably of thymic origin, including the case presently reported.

The difficulties in classification of thymic tumors stem from many causes. To begin with, the histogenesis of the normal gland is still subject to controversy and, consequently, interpretation of neoplastic cell types is subject to divergence (9). Epithelial neoplasms arising in the paramediastinal portions of the lung lobes and invading the mediastinum secondarily contribute to the problem. Teratoid tumors characteristically occupy a position in the mediastinum similar to the thymus. When the former undergo malignant change, it may be essentially unidirectional; the cell type then may recall epithelial tumors of the thymus and even seminoma of the testis (8). Widespread malignancy of the lymphatic system, such as lymphoma and Hodgkin's disease, may exist in the thymus as well as other sites. Indeed, there is no certainty that the predominant small round cell of the normal thymus gland is anything other than a lymphocyte; it has certain biologic responses in common. Finally, well-developed Hassall's corpuscles are seen in only a small fraction of thymic neoplasms (10).

Neoplasms recognized as of thymic origin tend to have certain gross characteristics. The lesions are, at least at first, discrete and encapsulated, sometimes rather heavily so. They are typically but not invariably located in the anterior and superior portion of the mediastinum closely investing the pericardium at some point. In the malignant varieties, extension is likely to be direct, with infiltration of such contiguous structures as the pericardium, great vessels, trachea, and pleural surfaces with or without the production of a pleural effusion. Hematogenous spread is quite rare, and remote lymphatic extension not common although it does occur.

After sectioning, the cut surface of thymic tumors may present many fibrous septa and

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[2] This study was aided by a grant from the Office of Naval Research, Project N6ori-44, Task Order XI.

trabeculations. Some tumors are densely solid; others are rather fleshy or soft in texture. Microcyst formation can occur. Sometimes very large cystic cavities are seen. The cyst contents are either clear and watery, sanguineous or putty-like in consistency and color. In the latter case a superficial resemblance to large caseous foci in the mediastinum, the so-called tuberculoma, exists (5).

The purpose of the following case report is to record an instance of grossly cystic thymic tumor which illustrates the possibility of confusion with tuberculoma, and which was also associated with minimal symptoms suggestive of myasthenia gravis.

CASE REPORT

M. L. W., New Haven Hospital #61524. The patient, a white, married female of fifty-one years, was admitted to the private medical service on January 19, 1943, with a complaint of pain in the left shoulder, left arm, and little finger of insiduous onset and several months' duration. Diabetes mellitus had been first diagnosed in 1937, and had been easily regulated by dietary measures without the routine use of insulin.

There was a history of scarlet fever in childhood. Marriage occurred twenty-seven years previous to this admission and resulted in three normal pregnancies. In 1930, a hysterectomy and bilateral salpingectomy had been performed because of menorrhagia, but no pathologic report was recorded.

The admission physical examination revealed a rectal temperature of 100°F., pulse rate of 100, and respiratory rate of 20 per minute. The patient did not appear ill. The chest was normal on examination except for a soft apical systolic murmur. Abdominal examination showed only the well-healed scar of a previous laparotomy in the suprapubic region. There was minimal hypertrophic arthritic change in the fingers of both hands. A routine neurologic examination was not remarkable.

Laboratory studies revealed a negative tuberculin (OT, 0.1 mg. at twenty-four hours), a nonprotein nitrogen of 26, and fasting blood sugar of 152 mg. per 100 ml. Roentgenograms of the chest for routine survey purposes revealed on the left side of the superior mediastinum a discrete, lobular, and homogeneous opacification, continuous with the left heart border (figure 1). In the lateral film, this density was situated anteriorly. Upon laminagraphy, the mass measured 9 cm. in diameter and did not appear to extend into the right side of the mediastinum or posteriorly. The radiologist's diagnosis was lymphoma.

Eight days after admission the patient had a slight and transient episode of left facial weakness, numbness of the left side of the face, slight difficulty in swallowing, and a tendency to choke on nasopharyngeal secretions during the night. A neurosurgical consultation the next day did not result in a definite diagnosis, but peripheral neuritis was suggested, perhaps on a diabetic basis. A surgical consultation was then requested, and operation was advised with a diagnosis of mediastinal tumor.

Operation was carried out on February 4, 1943, under endotracheal general anesthesia, using cyclopropane, nitrous oxide, and ether. A left submammary incision gave access to the fourth rib, which was resected in its anterior half together with the corresponding cartilage. Additional exposure was required and gained by transection of the third and second cartilages. A partly solid and partly cystic tumor was exposed, intimately adherent to the upper pericardium and in front of the great vessels. Numerous small blood vessels entered the capsule. After freeing the main tumor mass, a pyramidal extension into the superior mediastinum was dissected free. A single rather large arterial twig entered this upper pole. The lesion was removed in its entirety without entering the capsule. The pleural cavity was closed without drainage after aspirating residual air and fluid. One transfusion of 500 ml. of citrated blood was given.

The patient had a very uneventful convalescence, requiring one endotracheal aspiration and no thoracentesis. Prostigmin was administered daily in doses of 0.048 gm. until discharge upon the sixteenth postoperative day. The patient is well and without evidences of recurrence at the present time, a period of more than ten years.

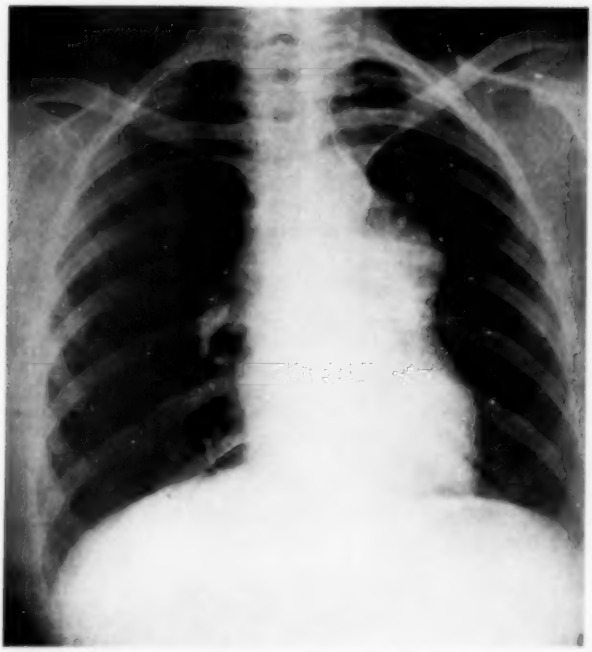

FIG. 1. Postero-anterior roentgenogram of the chest at time of admission, showing tumefaction confluent with left heart border.

Pathology: The gross specimen was a well-encapsulated, pear-shaped mass measuring approximately 10 cm. in its longest (vertical) axis, and weighing 106 gm. (figure 2*A*). The predominant color was a pinkish-gray. Upon sagittal section, a large spherical cyst was seen in the inferior half of the specimen. The cyst was filled completely with an odorless, grayish putty-like material showing no evidence of formed structures such as hair or teeth. The wall of the cyst was relatively smooth-surfaced and measured 2 to 8 mm. in thickness. The inferior pole of this cyst showed a single outpocketing which was somewhat hemorrhagic. The upper portion of the cut specimen revealed a series of smaller, mutually independent cysts containing bloody liquid and lined by a glistening smooth and thin membrane (figure 2*B*).

On microscopic section certain areas, rather diffusely distributed, were characteristic of involutional changes in adult thymic tissue. The wall of the largest and inferiorly placed cyst showed well-collagenized connective tissue, a scattering of lymphocytes, and occasional plasma cells. The smaller cysts were set in a stroma of less dense connective tissue and were lined with a flattened type of cell; the subepithelial layers showed a marked lymphocytic infiltration (figure 3). Throughout the stroma were scattered a few well-defined Hassall's corpuscles with central keratinizing whorls.

The frequent cystic dilatations were thought to have resulted from involutional changes in certain of the Hassall's corpuscles. Another more recent interpretation (7) considers them to be distended tissue or lymphatic spaces lined with primitive mesothelium (or endothelium).

The pathologic diagnosis was cystic thymoma.

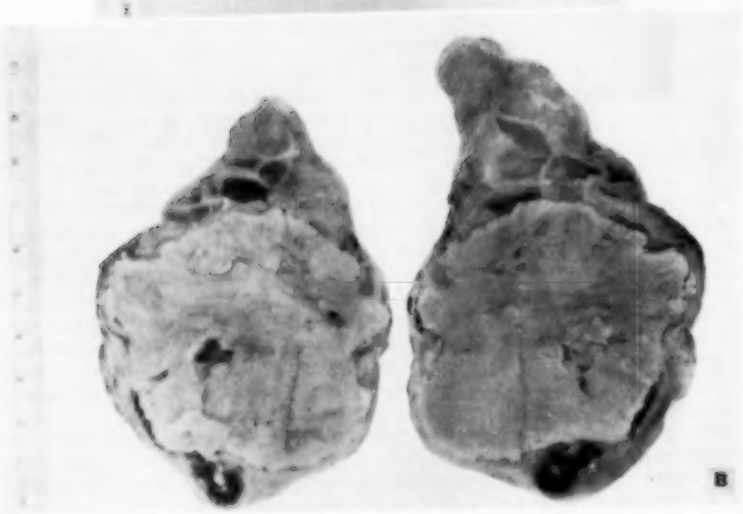

FIG. 2A. External appearance of excised specimen, demonstrating well-defined capsule.
FIG. 2B. Cut surfaces after longitudinal section of tumor. A large slightly irregular cavity is seen packed with grayish grumous material; also several smaller cysts, the fluid contents of which have escaped.

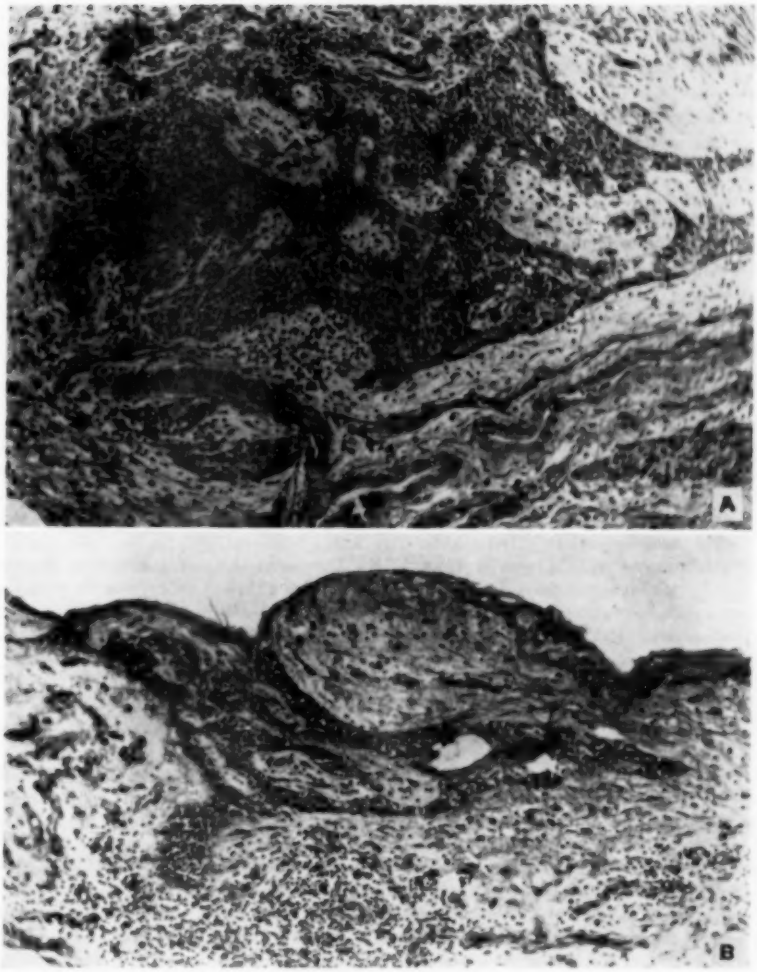

FIG. 3A. Microscopic section demonstrating a structure suggestive of atrophic thymus. This appearance is characteristic of many areas in the solid portion of the tumor.

FIG. 3B. Lining of a cyst which has developed in a mass of apparently atrophic thymic tissue, similar to that seen in figure 3A. Several smaller cysts are present below the major one. (Same magnification as in figure 3A)

COMMENT

Of some interest in this case are the very transient and mild evidences of myasthenia during the preoperative period. These included evanescent dysphagia and a tendency to choke on post-nasal secretions. Only after direct questioning did the patient admit also to some fatigue in the quadriceps femoris on climbing a flight of stairs. The transient left

facial weakness was also probably of significance, although the consulting neurologist was not sufficiently impressed to suggest a diagnosis of myasthenia. Nevertheless, these symptoms did not recur after excision of the lesion, and the patient noted subjective improvement in the postoperative period after small doses of prostigmin. The incidence of thymic tumors in cases of myasthenia gravis has been reported to be in the neighborhood of 15 per cent (3). Conversely, there is a wide divergence of opinion concerning the frequency of myasthenia among patients who harbor thymic tumors. Clagett and his coworkers (10), after a very large experience with thymectomy in myasthenia gravis, report an incidence of approximately 75 per cent. The case reported herein was the only one in the present writer's small group of thymic tumors with myasthenic manifestations, and these were of mild and transient character.

A review of certain reported cases of isolated "tuberculoma" in the anterior mediastinum shows a definite resemblance to the gross appearance of the specimen in the case reported here. The designation of "tuberculoma" should not be made unless tubercle bacilli can be demonstrated, preferably by culture, or the unmistakable histology is present in patients with a positive tuberculin. It is of significance that the large cyst with its putty-like contents in this case could not definitely be described as thymic until the more characteristic tissue around the smaller upper pole cysts was studied.

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TUBERCULOSIS IN THE VERY YOUNG[1, 2]

Report of Three Cases in Infants Less Than One Month of Age

EDWIN L. KENDIG, JR.

(Received for publication November 20, 1953)

Recovery from severe tuberculous infection in an infant less than one month of age is rare. Since report of a nineteen-day-old infant with widespread pulmonary tuberculosis in 1950, the writer has had occasion to treat 2 other tuberculous infants less than one month of age. One has apparently recovered, and the other died after an eight-month course of therapy. Follow-up observations on the first case and presentation of the other 2 cases comprises this report.

CASE REPORTS

Case 1 (follow-up observations). This previously reported, in 1950 (1), nineteen-day-old Negro female with widespread pulmonary tuberculosis (figure 1) received intramuscular streptomycin or dihydrostreptomycin for approximately ten months and Promizole® for approximately eight months.

She has had a stormy course subsequent to this time. She had otitis media and acute bronchitis several times. At two years of age she contracted pertussis and subsequently developed pneumonia. In October, 1951, a bilateral mastoidectomy was performed. Preoperative diagnosis was tuberculous mastoiditis but, while acid-fast organisms were demonstrated by direct smear, neither culture nor pathologic examination corroborated this finding.

The child is now more than five years of age. She is almost completely deaf. She appears to be mentally retarded, but this fall will enter a special school for the deaf, and later a more accurate evaluation of her intelligence can be made. The tuberculous process appears to be arrested.

Case 2. E. H., a one-month-old Negro male, was admitted to Dooley Hospital on April 28, 1951. He was delivered at St. Philip Hospital on March 27, 1951, and weighed 7 pounds, 1 ounce (3,203 gm.) at birth. He had been in good health until two days prior to admission. At that time he began to nurse poorly and vomited on several occasions. Just prior to admission, fever and a "hacking" cough appeared, and he was brought to Dooley Hospital.

Family history was contributory in that his mother was known to have tuberculosis and had been in a sanatorium for approximately one year from 1947 to 1948. Her disease at this time was supposedly arrested. One sibling had mediastinal tuberculosis in 1944, at the age of two years, but had apparently had no further activation of the disease.

At time of admission, physical examination revealed a subacutely ill 8-pound, 6.5-ounce (3,813 gm.) infant with rectal temperature of 101°F.; the pulse was 160 and respirations 60 to 80 per minute. His tongue was coated. Examination was otherwise negative except for harsh breath sounds over the left chest posteriorly and diminished breath sounds over the right chest posteriorly.

The tuberculin reaction (0.1 mg.) was positive, and a roentgenogram of the chest revealed areas of increased density in both hilar regions. Gastric washings were positive for tubercle bacilli on both smear and culture on three consecutive days. He was moderately anemic, with a hemoglobin of 9.5 gm. Cerebrospinal fluid examination revealed 5 leukocytes and a protein concentration of 63 mg. per 100 ml.

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[1] From the Department of Pediatrics, Medical College of Virginia, Richmond, Virginia.

[2] Presented in part at the annual meeting of the American Academy of Pediatrics, Miami, Florida, October 6, 1953.

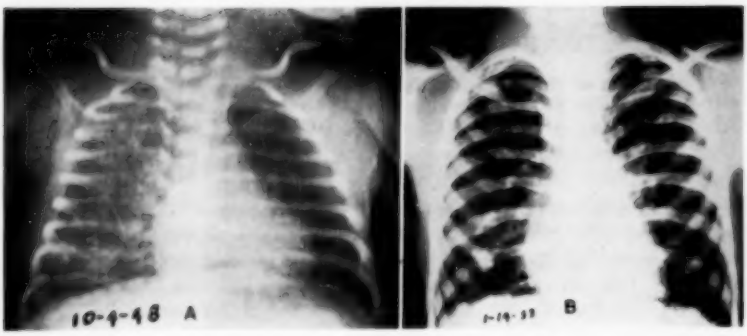

FIG. 1. *Case 1*

A. Widespread pulmonary disease, more extensive on right.
B. Calcific deposits in right lung field.

The patient was given dihydrostreptomycin, 200 mg. daily, for almost four months (August 17, 1951), when the dosage was increased to 300 mg. daily. Promizole, 0.5 gm. every eight hours, was administered during this period.

The patient clinically appeared to be progressing satisfactorily but gained little weight. A roentgenogram of the chest revealed increased disease with densities throughout the right lung and the medial half of the left lung on July 5, 1951 (figure 2). There was some clearing at the time of subsequent examinations.

On October 5, 1951, when the patient was six months of age, there was another elevation of temperature and the patient's general condition appeared to be worse. Cerebrospinal fluid examination revealed 52 leukocytes (50 lymphocytes) and a protein concentration of 45 mg. per 100 ml. Subsequent examinations revealed greater pleocytosis (308 leukocytes, with 96 per cent lymphocytes on November 13, 1951), and tubercle bacilli were demonstrated on both smear and culture of the fluid.

Intrathecal streptomycin, 50 mg. daily, was begun on October 5, 1951. Intramuscular dihydrostreptomycin was continued and, on November 15, 1951, the dosage was increased to 400 mg. daily. Promizole was continued in the dosage previously noted.

In spite of therapy, the patient's illness grew steadily worse; he developed hydrocephalus, and died on December 30, 1951, eight months following admission to the hospital.

Case 3. L. K., a Negro female, was delivered at the Louise Obici Hospital, Suffolk, Virginia, on April 20, 1952, and weighed 5 pounds, 9 ounces (2,523 gm.) at birth. The mother was known to have miliary tuberculosis. The baby was mistakenly put to breast one time within twenty-four hours after delivery, but after that time was kept isolated from the mother.

The patient was well until May 13, 1952, when she had a slight temperature elevation, which reached a maximum of 101°F. (rectal) two days later. Physical examination was negative at that time. Tuberculin patch test was positive, and smear of gastric washings revealed the presence of acid-fast bacilli. A roentgenogram of the chest showed heavy hilar densities and an area of increased density in the left lung base (figure 3).

Treatment consisting of streptomycin, 75 mg. twice daily, was instituted and continued until June 16, 1952. Three days later, isoniazid, 12.5 mg. daily, was begun and this was continued until the patient was admitted to Dooley Hospital, Medical College of Virginia, on July 21, 1952.

At time of admission the baby was three months of age and weighed 9 pounds (4,082 gm.) Physical examination revealed an occasional wheeze over the right lung field. Except for an umbilical hernia, examination was otherwise negative.

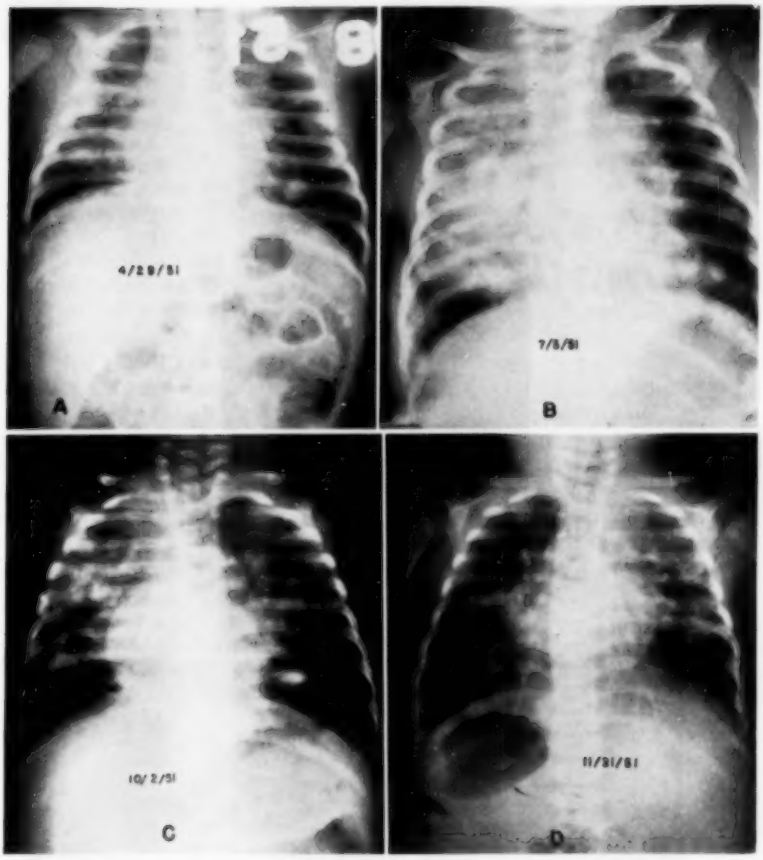

FIG. 2. *Case 2*

A. Increased hilar densities, bilateral; few nodules in lung parenchyma.

B. Increased disease with densities throughout right lung and medial half of left lung.

C. Some clearing of disease process.

D. Marked clearing of disease process in right lung, with increased densities in left upper lung field.

The patient's temperature was 100°F. (rectal). A roentgenogram of the chest revealed essentially the same abnormalities noted previously except for the appearance of nodular densities in the right lung base. Intramuscular streptomycin, 240 mg. daily, and isoniazid, 16 mg. daily, were begun.

Since that time the patient has progressed satisfactorily. Subsequent chest roentgenograms have showed clearing of the lung lesion. Streptomycin therapy was discontinued after three months but isoniazid was continued until May 9, 1953.

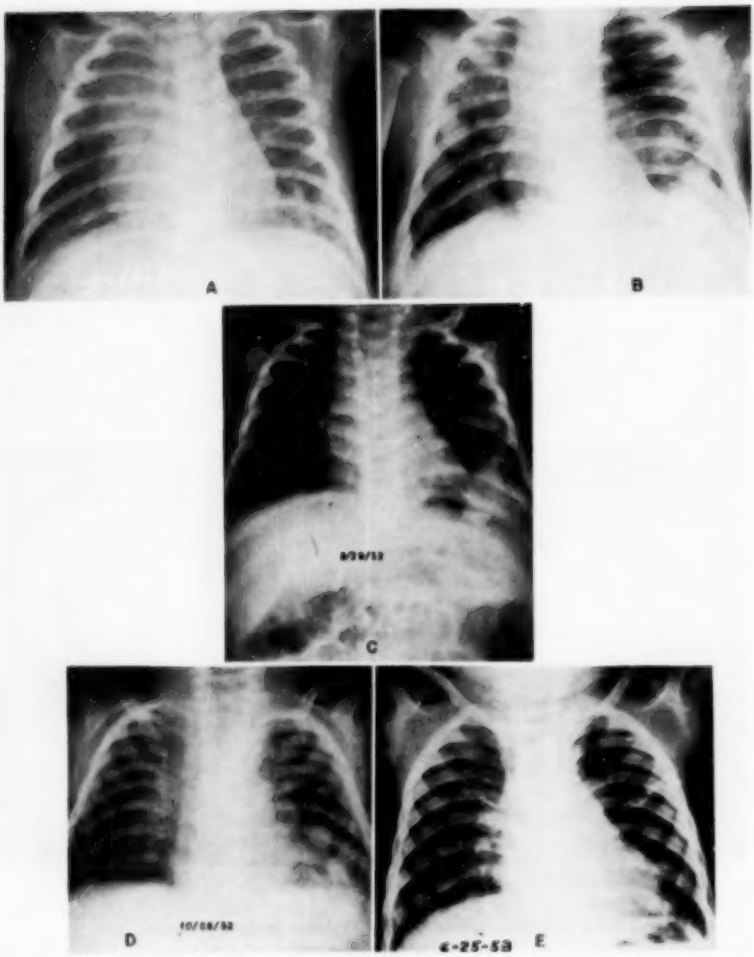

FIG. 3. *Case 3*

A. Heavy hilar densities with areas of increased density in left lung base.
B. As in *A*, with addition of nodular densities in right lung.
C. Marked clearing; density in left lung base persists.
D. Density in left lung base is clearing.
E. Complete clearing of disease process.

COMMENT

The foregoing cases constitute an unusual group. Tuberculous infection of this severity in infants less than one month of age is practically always fatal. Two of these infants survived, and the other lived eight months before succumbing to the disease.

In so far as present knowledge is concerned, it may be said that these patients were

not treated to the best advantage. However, as no such cases had been reported, a satisfactory therapeutic approach had to be determined by trial. There are several important lessons to be learned.

In *Case 1* (R. K.), streptomycin was continued longer than was probably necessary. Further, it is doubtful whether intrathecal streptomycin was indicated at all. These two points undoubtedly were contributory to the deafness and, perhaps, to the mental retardation. In spite of it, as far as can be determined, this remains the youngest recorded case of widespread pulmonary tuberculosis with survival. Recovery might not have been effected had the course of streptomycin been shorter.

In *Case 2* (E. H.), the causative organism apparently became refractory to streptomycin. Tuberculous meningitis made its appearance after five and one-half months of streptomycin therapy. From that time the illness was steadily progressive. While such severe tuberculous infection in a one-month-old infant clearly indicated the use of streptomycin, the result does illustrate the fact that streptomycin therapy cannot be used as prophylaxis against tuberculous meningitis and that its use in uncomplicated primary tuberculosis is unwarranted.

The last patient (L. K.) did not exhibit the degree of pulmonary pathology shown in the first two patients. She responded satisfactorily to therapy. This case demonstrates the well-known fact that a child born of a tuberculous mother must be kept isolated from her until the disease has been shown to be no longer active. Since the primary focus was in the lung parenchyma, congenital tuberculosis seems unlikely. While the infant may well have aspirated infected amniotic fluid, the possibility that contact with the mother was the source of the infection must be seriously considered.

SUMMARY

Three cases of tuberculosis in infants less than one month of age are reported. Two of the 3 patients survived, and the other lived eight months after therapy was instituted.

SUMARIO

La Tuberculosis en los Lactantes Muy Pequeños: Presentación de Tres Casos de Menos de Un Mes de Edad

Descríbense 3 casos de tuberculosis en criaturas de menos de un mes de edad. Dos de los 3 enfermitos sobrevivieron y el otro vivió hasta ocho meses después de iniciarse la terapéutica.

RESUME

Tuberculose chez le nourrisson: Rapport sur trois cas chez le nourrisson au-dessous d'un mois

Trois cas de tuberculose chez des nourrissons âgés de moins d'un mois sont rapportés. Sur trois malades, deux ont survécu, l'autre a vécu huit mois après l'instauration du traitement.

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TORSION OF THE SPLEEN ASSOCIATED WITH PNEUMOPERITONEUM

WILLIAM H. FALOR[1] AND DARREL C. ANGUS

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INTRODUCTION

The value of pneumoperitoneum as definitive or complementary therapy in the management of pulmonary tuberculosis has been enhanced by the rarity of complications attending the procedure. Middleton (1) in 1950 added torsion of the spleen to the list of complications. Torsion of the splenic pedicle will develop only in the presence of abnormal mobility of the spleen. The factors concerned in its abnormal mobility are both congenital and acquired.

The *congenital factors* in torsion of the splenic pedicle are chiefly the length of the pedicle and the conformation of the abdominal cavity. In the development of the peritoneal attachments, embryologic changes determine the length of the splenic pedicle (figure 1). The stomach (before rotation) is attached posteriorly (figure 1*a*) by a dorsal mesogastrium and anteriorly by a ventral mesogastrium. The spleen originates as a localized cellular collection in the left layer of the dorsal mesogastrium. These cellular collections fuse with one another to form a lobulated spleen, the notch or notches of which are the only surface traces of lobulation in the adult organ.

The spleen divides the dorsal mesogastrium into: a gastrosplenic part and a spleno-aortic part (lienorenal ligament). As growth takes place (figure 1*a* and *b*), the spleen and the stomach shift to the left and the liver shifts to the right. The spleno-aortic ligament is pushed against the posterior abdominal wall and a fusion takes place between the two opposed surfaces. The spleno-aortic ligament having been pulled to the left comes in contact with the left kidney and because of its new position is referred to as the lienorenal (splenorenal) ligament (figure 1 *cdult*). If fusion to the posterior wall fails to occur, the stabilizing splenorenal ligament will be absent and the spleen will be abnormally mobile. The surgeon recognizes the immobilizing effect of an intact splenorenal ligament and considers the key step in splenectomy to be incision into the left leaf of this structure; this maneuver allows easy access to the splenic pedicle.

Abell (2) suggests that prolapse of the spleen may be more common in the person with an asthenic body habitus because of the relative reversal of normal intra-abdominal pressure relationships. In such a person the acute angle of the costal margin together with decreased lower thoracic circumference create a small upper abdominal surface area for distribution of pressure. As a result more pressure is directed toward the lower abdomen, and upper abdominal viscera tend to be forced downward.

The *acquired factors* concerned with abnormal splenic mobility may be grouped under two headings: increased weight of the spleen, and conditions bringing about relaxation of the abdominal wall and of the splenic ligaments. Of 116 cases of torsion of the spleen reported by Abell (2) and Bohrer (3), 31 had splenic enlargement secondary to malaria. It is assumed that malarial splenomegaly was the predisposing cause of this latter group. It is questionable, however, whether the weight of the spleen was the prime factor, for in the remaining 85 cases there was no apparent splenomegaly.

Of 101 cases of torsion of the spleen in women (2, 3), 55 were pregnant or in the puerperium and 35 had borne two to fourteen children. Thus, it would appear that flaccidity

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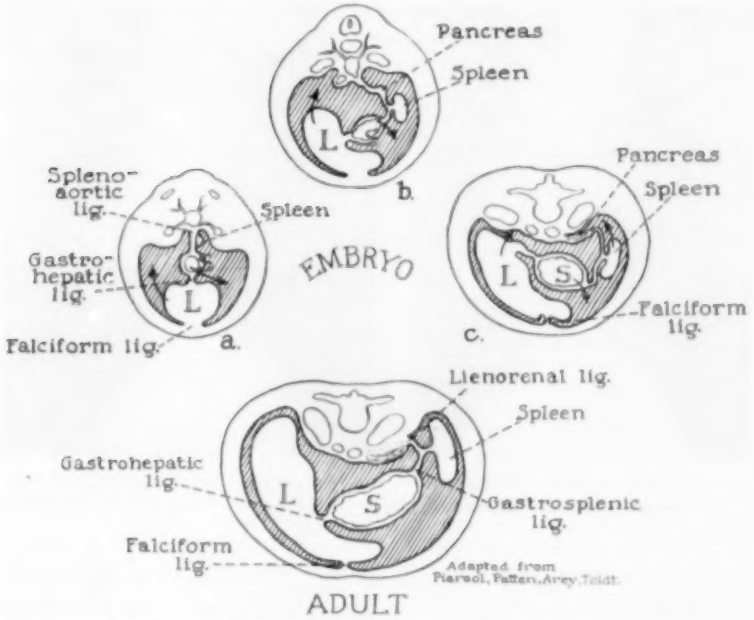


FIG. 1. The embryologic development of the splenic pedicle.

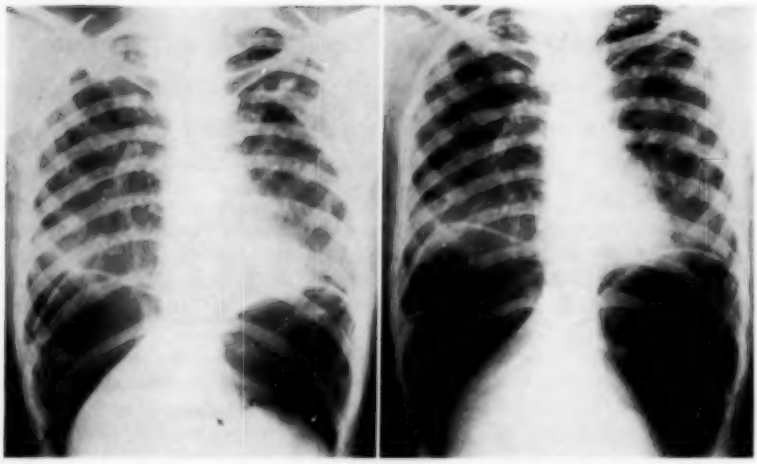
and relaxation of the abdomen resulting from repeated pregnancies favor torsion of the spleen.

Prolonged artificial pneumoperitoneum employed in the management of pulmonary tuberculosis is the cause of roentgenographically visible ptosis of the upper abdominal viscera and creates more free space in which these organs may be moved. The spleen commonly may be identified lying below its normal subphrenic location (figures 2 and 3). Such dislocation can only have occurred by stretching, attenuation, and possibly rupture of the splenorenal and phrenocolic ligaments.

As the splenic attachments elongate, the splenic pedicle is progressively stretched and narrowed until it is but a stalk holding a freely mobile spleen. This advanced degree of change in the splenic supports must be rare or vulvulus of the spleen would be a common disease. Several congenital and acquired factors must be coexistent before pneumoperitoneum can precipitate torsion of the spleen.

In a review of 116 cases of torsion of the spleen (2, 3), 34 different preoperative diagnoses were made. Approximately 65 per cent of the cases occurred in persons between the ages of twenty and forty; 87 per cent of the cases occurred in women.

The symptoms of the acute attack of splenic torsion are not pathognomonic of the abnormality but are those common to an intra-abdominal catastrophe in which massive tissue necrosis is present. Pain in the left upper quadrant, nausea, vomiting, and elevation of pulse, temperature, and leukocyte count are usually present. The only diagnostic physical sign is the finding of a rather freely movable, tender abdominal mass possibly located in the left upper quadrant but which could equally well be almost any place within



FIGS. 2 and 3. *Case 1*. R. M. Pulmonary tuberculosis treated with pneumoperitoneum. (Left) Roentgenogram demonstrating ptosis of the spleen. (Right) Post-splenectomy roentgenogram.

the abdominal cavity. The use of roentgenograms of the abdomen in several positions is of considerable diagnostic help for confirmation of the physical finding of the movable mass (Figure 4).

CASE REPORTS

Case 1. R. M., a 26-year-old white nulliparous female, was admitted to The City Hospital of Akron on June 4, 1952, complaining of excruciating constant pain localized in the left upper abdominal quadrant. The pain was of four hours' duration, had developed rapidly, and was constantly increasing in degree. The previous systemic history was irrelevant except for an eleven-year history of pulmonary tuberculosis. Pneumoperitoneum (figure 2) had been given for the previous twenty-one months through needle wounds in the left upper mid-abdomen. Physical examination revealed a well-developed, well-nourished young female lying restlessly in bed complaining bitterly of abdominal pain. The abdomen was tympanitic, with air in the peritoneal cavity, was moderately tender, with deep left upper quadrant pressure, but contained no palpable organs or masses. The temperature was 99°F. and the pulse was 66 per minute. Urinalysis was normal; blood count was 3,840,000 erythrocytes and 11,000 leukocytes per cu. mm., with 81 per cent polymorphonuclears, 16 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophils. The coagulation time was three and one-half minutes; bleeding time, two and one-fourth minutes, and the prothrombin time was 23 per cent of the normal values. Two days postoperatively the prothrombin time had risen to 68 per cent of normal. No vitamin K was administered in the interim, and the patient had not received streptomycin therapy in the preceding twelve-month period.

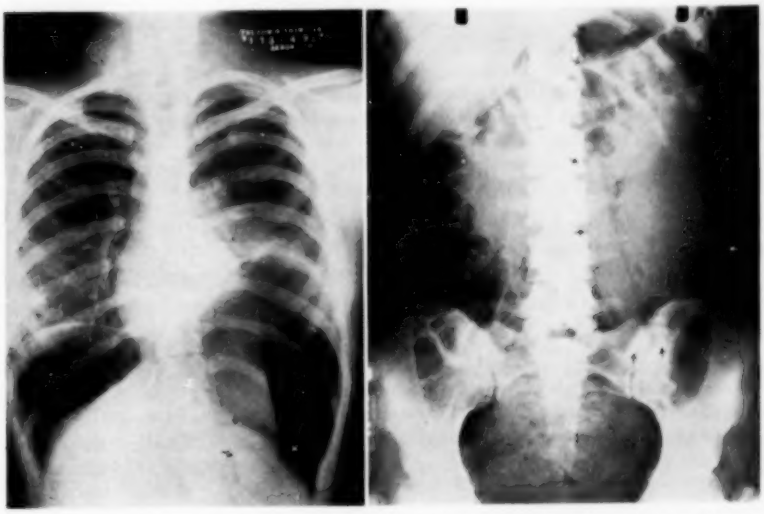
A diagnosis was made of "necrosis of intra-abdominal tissue," and a laparotomy was performed through a mid-epigastric incision. The spleen was the only abnormal organ, weighing 500 gm. and being approximately three times the anticipated normal size. It was black and completely infarcted because of a 540-degree counterclockwise rotation on the gastro-splenic ligament. The splenic pedicle measured 5 cm. in length, 4 cm. in width, and 2 cm. in thickness, and contained both the short gastric and splenic vessels. The pedicle

was the only attachment of the organ to the adjacent viscera. The spleen was readily untwisted, but signs of viability did not appear and splenectomy was performed. The histologic appearance was that of chronic passive congestion. The patient was discharged on her seventh postoperative day after an uneventful convalescence. Pneumoperitoneum was resumed (figure 3).

Case 2. J. M., a 20-year-old white primida gravida, was admitted to The City Hospital of Akron on July 27, 1953, complaining of agonizing left upper quadrant pain. The pain began three days prior to admission, was of progressively increasing intensity, and was accompanied by chills and fever. Previous systemic history was negative except for a four-year history of pulmonary tuberculosis treated by sanatorium care from September, 1949, to February, 1951. Pneumoperitoneum assisted by left phrenic paralysis (figure 4) was administered from February to September, 1951, and the disease was considered to be arrested.

On July 11, 1953, sixteen days prior to the present admission, a low caesarian section was performed on the patient because of abruptio placenta. She was delivered of a healthy living child and left the hospital on her sixth postoperative day after an uneventful recovery.

On the present admission, physical examination revealed an acutely ill young female patient complaining of severe left upper abdominal pain. Examination was otherwise normal except for an exquisitively tender, indefinable, large, slightly mobile mass lying in the left upper mid-abdomen. Mobility was best demonstrated by rolling the patient from side to side. A flat plate roentgenogram of the abdomen (figure 5) showed a large mass obscuring the left psoas major muscle shadow. The temperature was 102°F.; pulse, 92 per minute; and the blood pressure, 118 systolic and 76 diastolic in mm. of mercury. Urinalysis was normal; blood count was 3,200,000 erythrocytes and 11,700 leukocytes per cu. mm., with 73 per cent polymorphonuclears, 25 per cent lymphocytes, 1 per cent monocytes, and



FIGS. 4 and 5. *Case 2.* J. M. Pulmonary tuberculosis treated with pneumoperitoneum. (Left) Roentgenogram demonstrating ptosis of the spleen. (Right) Flat plate of abdomen showing a large mass (spleen) partially obscuring the left psoas major muscle.

1 per cent eosinophils. The coagulation time was three minutes; bleeding time, 1 minute; and the prothrombin time was 54 per cent of the normal values. No streptomycin had been administered in the preceding twelve months.

A diagnosis was made of "possible foreign body in the abdominal cavity subsequent to caesarian section or possible delayed rupture of the spleen," and laparotomy was performed through a left upper abdominal transverse incision.

The spleen was the only abnormal organ, weighing 880 gm.; it was black, nonviable, and only moderately enlarged, but on its anteromedial surface was a huge subcapsular hematoma which was black in color and constituted the main mass. The splenic pedicle measured 5 cm. in length, 4 cm. in width, and 3 cm. in thickness, and was the only supporting structure. The spleen had become rotated clockwise through 900 degrees; after reduction of the volvulus the organ was still nonviable, and splenectomy was performed.

Histologic diagnosis was "marked congestion of the spleen." When first visualized, the veins of the gastrocolic omentum and of the transverse mesocolon were markedly engorged; it was estimated that the venous pressure in these vessels was at least twice the anticipated normal. The constantly enlarging spleen exerted considerable traction on the entire portal system. This attenuation of the portal vein caused an increase of the peripheral pressure in the portal tributaries. As soon as splenectomy had been performed, these previously engorged vessels assumed a normal caliber. Convalescence was not remarkable except for increased vaginal bleeding, and the patient was discharged on her seventh postoperative day.

SUMMARY

Two cases of volvulus of the spleen which occurred in tuberculous patients treated by pneumoperitoneum are presented, and the causal relationship of pneumoperitoneum is considered. The rarity of this complication is consistent with the over-all low morbidity associated with pneumoperitoneum.

SUMARIO

Torsión del Bazo Asociada con Neumoperitoneo

Preséntanse 2 casos de vólvulo esplénico observados en tuberculosos tratados con el neumoperitoneo y se considera la relación etiológica del último. La rareza de esta complicación es compatible con la baja morbidad global que acompaña al neumoperitoneo.

RESUME

Torsion de la rate associée au pneumopéritoine

Présentation de deux cas de volvulus de la rate survenus à la suite de la création d'un pneumopéritoine; les rapports étiologiques avec le pneumopéritoine examinés. La rareté de cette complication s'accorde avec le faible taux de morbidité globale du pneumopéritoine thérapeutique.

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LÖFFLER'S REACTION TO PARA-AMINOSALICYLIC ACID[1]

HERMAN TUCHMAN

(Received for publication January 13, 1954)

Numerous and varied reactions have been attributed to para-aminosalicylic (PAS) acid since its introduction as an antituberculous agent by Lehmann in 1946. Acute drug fever and urticaria are the common allergic manifestations, while other toxic effects appear mainly to be confined to the gastrointestinal tract, presumably a result of local irritation. Warring and Howlett (1), in describing allergic reactions to PAS, presented one case of a 33-year-old white woman with an allergic diathesis who developed acute bilateral pneumonitis with eosinophilia while being treated with this drug.

A review of the literature reveals the rarity of pulmonary reactions as a part of hypersensitivity to PAS (2). The present report is concerned with a patient who developed roentgenographic evidence of acute bilateral pneumonitis and eosinophilia while being treated with PAS in conjunction with streptomycin for pulmonary tuberculosis. The syndrome was repeated by giving a test dose of PAS.

CASE REPORT

J. C., a 21-year-old white male, was admitted to Madison Veterans Administration Hospital on March 31, 1953, as a transfer patient from the Hines Veterans Administration Hospital, Illinois, with a diagnosis of pulmonary tuberculosis, minimal, active.

The patient had entered Hines Hospital on January 14, 1953, with a complaint of anorexia and severe cough. He had been awakened from his sleep two days before with coughing paroxysms productive of only small amounts of green sputum. Substernal discomfort occurred with the cough, but the patient noted no other symptoms. The systemic review was essentially negative. There was no allergic history. The patient stated that his father was admitted to a tuberculosis sanatorium one week previous to the patient's admission to Hines.

Physical examination revealed an acutely ill white male who had a temperature of 103.4°F., and a pulse of 120 per minute. A few rhonchi were heard in the extreme lung bases, but the remainder of the physical examination was normal. The admission hemogram showed a hemoglobin of 14.5 gm., with an erythrocyte count of 4,720,000 per cu. mm. The leukocyte count was 6,300 per cu. mm., with 70 per cent neutrophils, 27 per cent lymphocytes, 1 per cent monocytes, and 2 per cent eosinophils. Three sputum smears were negative for acid-fast bacilli. The roentgenographic diagnosis was minimal pulmonary tuberculosis. A chest roentgenogram on January 16 revealed only an irregular infiltration which on lordotic view proved to be a nodular lesion at the left first anterior interspace with increased peribronchial markings extending from it inferiorly to the left hilum. Sputum cultures were positive for tubercle bacilli. Diagnostic bronchoscopy was performed, and the tracheobronchial tree was found to be normal. The patient was then transferred to this hospital on March 31, 1953, for treatment of the pulmonary tuberculosis, and on admission the patient was asymptomatic.

Physical examination revealed a well-developed, thin, white male who appeared his stated age and who did not appear to be ill. His temperature was 98°F. and the pulse was 70 per minute. The lungs were clear, and the remainder of the physical examination was within normal limits.

Laboratory work revealed a normal urinalysis. The hemoglobin was 15.8 gm., and the

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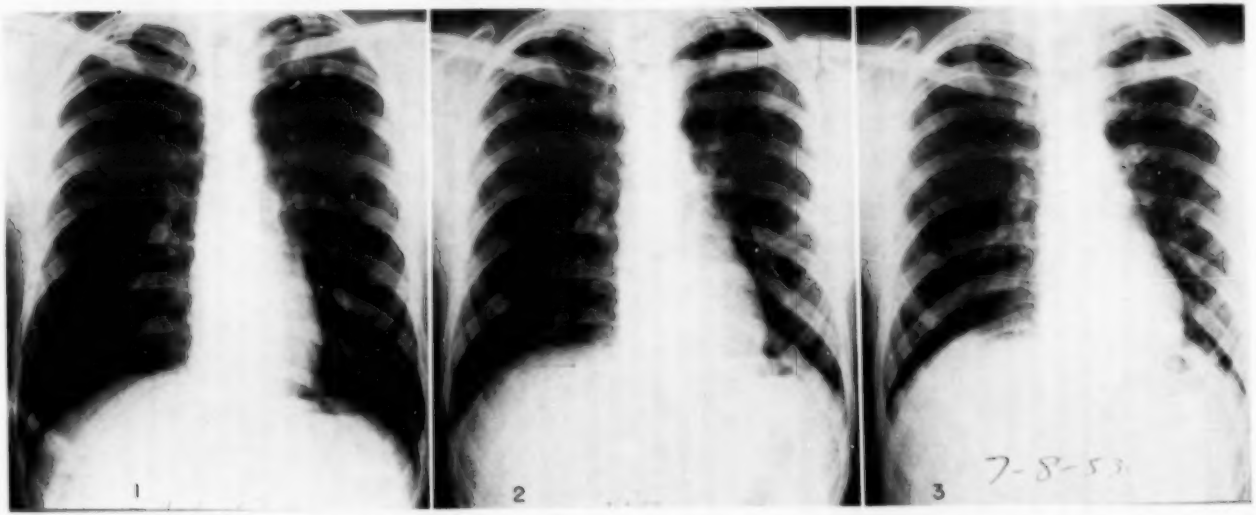

FIG. 1. Stereoscopic chest roentgenogram, showing in the left upper lung field an infiltrative area of disease in the posterior portion of the apicoposterior segment, projecting into the first anterior interspace.

FIG. 2. Chest roentgenogram of July 3, 1953, showing for the first time what appear to be a spread of the infiltrative disease in the right lung laterally in the first anterior interspace. Some spread of disease throughout the lateral portion of the left upper lobe also seems to be present.

FIG. 3. Chest roentgenogram of July 8, 1953, showing no further spread of disease.

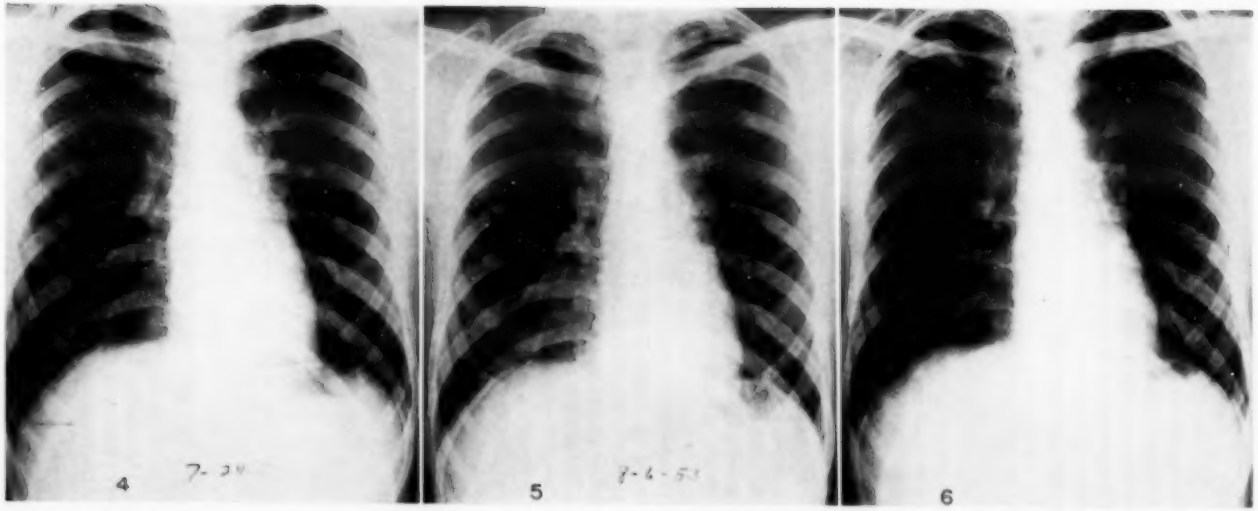

FIG. 4. Chest roentgenogram of July 24, 1953, showing complete resolution of the infiltrative process.

FIG. 5. Chest roentgenogram of August 6, 1953, taken twenty-four hours after the discontinuance of PAS therapy, showing reappearance of the infiltrative processes in both upper lung fields.

FIG. 6. Chest roentgenogram of August 12, 1953, showing resolution of the infiltrative process.

leukocyte count was 7,600 cu. mm., with 61 per cent neutrophils, 33 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. A sputum culture on April 2 was positive for tubercle bacilli. A stereoscopic chest roentgenogram (figure 1) revealed the right lung to be free of parenchymal disease. In the left lung there was an infiltrative area of disease in the posterior portion of the apicoposterior segment, projecting into the first anterior interspace. There was a moderate amount of fibrosis extending from this lesion to the hilum, and several firm strands of fibrous density were present in the apical portion of the apicoposterior segment. The patient was placed on Class II exercise tolerance, and on April 4 was started on para-aminosalicylic acid, 4 gm. three times daily, and streptomycin, 1 gm. twice weekly.

Initially, he showed no untoward reactions to his medications, and a subsequent chest film taken on May 29 showed the disease in the left upper lobe to be stable. However, on June 16, eight weeks following the institution of therapy, the patient began to show persistent hyperpyrexia. The temperature hovered about 99°F., with occasional abrupt rises to 102°F. He also complained of severe frontal headache, anorexia, and increase in cough with no apparent increase in sputum. Physical examination of the chest was essentially normal, and there was no evidence of upper respiratory tract infection. A chest roentgenogram on July 3 (figure 2) revealed for the first time what appeared to be a spread of the infiltrative disease in the right lung laterally in the first anterior interspace. There also seemed to have been some spread throughout the lateral portion of the left upper lobe, with mottled density to the level of the fourth and fifth anterior interspaces. A leukocyte count showed 10,400 cells per cu. mm., with 53 per cent neutrophils, 31 per cent lymphocytes, 5 per cent monocytes, and 12 per cent eosinophils. Oxytetracycline (Terramycin), 250 mg. daily, was given for five days in an attempt to curb a possible intercurrent infection.

The patient continued to complain of headache and persistence of a dry, hacking cough. A chest roentgenogram on July 8 (figure 3) revealed no further spread of the disease. A differential blood count on July 7 revealed 26 per cent eosinophils.

On July 9 it was decided to discontinue the PAS to see if this drug might be responsible for the eosinophilia. The patient immediately improved subjectively. His appetite returned and his headaches disappeared, as did the afternoon hyperpyrexia. Sputum smears were negative for eosinophils. A leukocyte differential count on July 10th showed 1 per cent eosinophils. Chest roentgenograms on July 10 showed clearing of the infiltration first noted on June 26, and another film on July 24 (figure 4) showed complete resolution of the process.

Streptomycin was given as before, 1 gm. twice weekly, until August 4. It was decided to test the patient's reaction to PAS. Calcium PAS (Parasal) in tablet form was administered. The patient received a total of 16 gm. in a twenty-four-hour period. The temperature rose to 101°F. He complained of headache, nausea, and noted recurrence of a severe, hacking cough. On August 6, a leukocyte count revealed a total of 14,500 cells per cu. mm., with 11 per cent eosinophils. On August 7, this count was 9,600 per cu. mm., with 16 per cent eosinophils. A chest roentgenogram on August 6, (figure 5), twenty-four hours after stopping the PAS, revealed reappearance of the infiltrative processes in both upper lung fields. A leukocyte count on August 10 showed a total of 8,400 cells per cu. mm., with 5 per cent eosinophils, and a roentgenogram on August 12 (figure 6) showed resolution of the process.

It was believed that this test dose proved the patient's hypersensitivity to PAS. On August 13, the patient was given 100 mg. of isoniazid three times daily in association with the streptomycin dosage. The patient has since been asymptomatic, and further chest roentgenograms have shown clearing of the original disease. He is now awaiting operation for segmental resection of the remaining tuberculous disease.

SUMMARY

An interesting and unusual response to para-aminosalicylic acid (PAS) occurred in a patient being treated with this medication for pulmonary tuberculosis. Initially, the chest

roentgenograms suggested either spread of the primary disease process or an intercurrent acute bilateral pneumonitis. Oxytetracycline (Terramycin) was administered in an attempt to allay the process. The appearance of marked eosinophilia (26 per cent) suggested an allergic reaction. Withholding the PAS resulted in clearing of the lung fields roentgenographically, and the eosinophilia disappeared. Reinstitution of treatment with a different form of the medication (calcium PAS in tablet form) was followed by recurrence of the allergic phenomenon. This course was interpreted as representing Löffler-type reaction to PAS therapy.

A patient who shows an apparent exudative spread of his tuberculosis while under therapy with PAS should be suspected of having developed an allergic reaction to the drug. Marked eosinophilia is a confirmatory sign. The diagnosis in the present case was established by re-provoking the syndrome when PAS was given as a test dose.

SUMARIO

Reacción de Löffler al Acido Para-Aminosalicílico

En un enfermo en vías de tratamiento con ácido para-aminosalicílico (PAS) por tuberculosis pulmonar, observóse una reacción interesante y extraña a dicha medicación. Al principio, las radiografías torácicas sugerían bien difusión del proceso morboso primario o una neumonitis bilateral aguda intercurrente. Tratando de aliviar el proceso, se administró oxitetraciclina (Terramicina). La aparición de eosinofilia acentuada (26 por ciento) sugirió una reacción alérgica. La suspensión del PAS fué seguida de despejo radiográfico de los campos pulmonares, desapareciendo la eosinofilia. La reiniciación del tratamiento con una forma distinta de la medicación (PAS cálcico en tabletas) fué seguida de reaparición del fenómeno alérgico. Esa evolución fué interpretada como reacción tipo Löffler a la terapéutica con PAS.

En un enfermo que revele aparente difusión exudativa de su tuberculosis mientras se halle bajo tratamiento con PAS debe sospecharse aparición de una reacción alérgica a la droga. Una eosinofilia acentuada constituye un signo corroborador. En el caso actual, se estableció el diagnóstico provocando de neuvo el síndrome con la administración de PAS como dosis de ensayo.

RESUME

Réaction de Löffler à l'acide para-aminosalicylique

Une réaction intéressante et inhabituelle à l'acide para-aminosalicylique s'est produite chez un malade traité par ce mèdicament pour une tuberculose du poumon. Initialement, les clichés du poumon suggéraient soit une extension de la primo-infection, soit une pneumonie bilatérale aigue. L'oxytétracycline (Terramycine) fut administrée pour tenter de juguler le processus. Une éosinophilie marquée (26%) suggérait l'allergie. La suppression du PAS a produit l'éclaircissement de l'image des chaps pulmonaires et la disparition de l'éosinophilie. La répétition du traitement avec une nouvelle forme de la médication (PAS calcique en comprimés) fut accompagnée d'une récurrence des phénomènes allergiques. Cette évolution est interprétée comme représentant une modalité de la réaction de Löffler au traitement par le PAS. Lorsque, au cours d'un traitement par le PAS, il se produit chez un malade une diffusion de la tuberculose à forme d'exudat, il y a lieu de penser à une réaction allergique au médicament. La présence d'une éosinophilie marquée est un signe confirmatif. Dans le cas actuel, le diagnostic a été établi en reproduisant le syndrome en administrant comme test une nouvelle dose de PAS.

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Notes

AN AGITATOR FOR BACTERIOLOGIC SPECIMENS

The mechanical agitation of sputum and body fluid specimens for tuberculosis examination has become a well-established procedure. Vigorous agitation virtually homogenizes the specimen, allowing for adequate centrifugation, control of contaminating organisms, more even distribution of tubercle bacilli, a decrease in treatment time, and a reduction in concentration of sodium hydroxide from 4 to 3 per cent. Steenken and Smith[1] recommended a paint shaker for use as an agitator. This machine has the disadvantage of necessitating special mounting, such as anchoring to a concrete block in order to hold the machine and to reduce vibration. Because of this special mounting, installation in many laboratories is very difficult or not feasible. Moreover, it is difficult to shield this shaker for protection from aerosols.

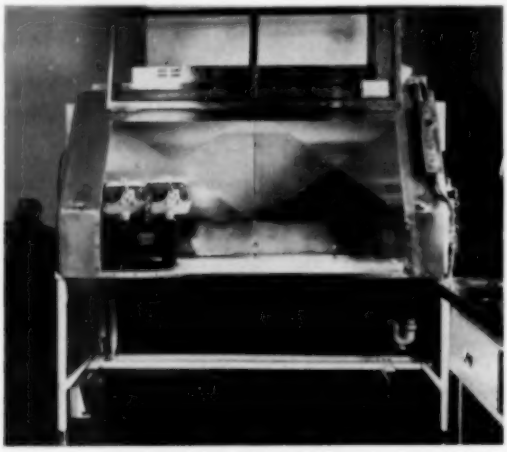

FIG. 1. Agitator for bacteriologic specimens

With the realization of the potential aerosol hazards to personnel resulting from high-speed agitation of contaminated materials, a different type of paint shaker[2] was adopted for laboratory use. This shaker requires no special mounting, is portable, and can be satisfactorily placed in a bacteriologic safety hood (figure 1).

To use this shaking apparatus, specimens are transferred to 120 cc. round, wide-mouth bottles, using a No. 9 regular rubber stopper. The bottles are metal protected against breakage by placing each in two cans (3 inches high by 2.5 inches in diameter) having a circle of 1-inch thick foam rubber in the bottom of each can. (Mallinkrodt ether cans with top removed work very well.) The foam rubber supplies tension to hold bottles in the adapters used on the shaking machines. Four metal-clad bottles are placed in each

[1] STEENKEN, W. JR., AND SMITH, M. M.: J. Lab. & Clin. Med., 1942, *27*, 1582.

[2] Harbil Paint Mixer, Model HB-7, manufactured by Harbil Manufacturing Co., 325 W. Ohio Street, Chicago 10, Illinois.

FIG. 2. Integral parts of adapters used on the shaking machine

adapter, and the adapters are then placed in the cradles and anchored in place with tightening screws. The adapters are constructed of sheet metal and are 7 inches wide, tapering to 2 inches on the bottom, 6 inches long, and 4.5 inches deep. These adapters are removable and, with the cans, will withstand repeated autoclaving for sterilization. Integral parts are illustrated in figure 2. Four specimens can be shaken in each adapter, or eight at one time. Four specimens can be shaken on one side of the machine with no counterbalancing necessary. A ten-minute shaking period is utilized. The shaker oscillates at approximately 800 oscillations per minute. No leakage or breakage has occurred in several months' usage. The results have been comparable to those obtained with the paint shaker as recommended by Steenken and Smith.

In summary: A shaking apparatus for agitation of bacteriologic specimens suitable for installation in a bacteriologic safety hood and requiring no special mounting is described.

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January 25, 1954

Correspondence

PROGNOSIS AND LONG-TERM CHEMOTHERAPY IN TUBERCULOSIS

To the Editor of the American Review of Tuberculosis:

The data presented by DeFriez and associates in the January 14, 1954, issue of the *New England Journal of Medicine* (page 250) are of extraordinary interest. In a twenty-year follow-up study of 377 patients treated for pulmonary tuberculosis with strict bed rest, they found a cumulative relapse rate of *50.1 per cent* at twenty years. Although the majority of relapses occurred within the first five years, the possibility of relapse after this date is by no means small; their tables indicate that 16 per cent of all relapses occurred five to ten years later, and an additional 10 per cent occurred ten to twenty years later. These figures re-emphasize the difficulties encountered in long-term prognosis. Many patients with pulmonary tuberculosis are permanently cured, but the problem, unsolved to this moment, is to predict which ones they will be.

The paper referred to deals with patients treated in the pre-chemotherapy era. This was the case also in Mitchell and Knudson's report on the results of bed-rest treatment for *minimal* pulmonary tuberculosis (Am. Rev. Tuberc., 1950, *61*, 809), in which the cumulative incidence of "reactivation" during treatment and for seven years following discharge was 37 per cent. With drug therapy we can expect a reduction in the frequency with which early relapse occurs, but many late relapses are now being seen in patients who were treated with antimicrobial agents for relatively short periods of weeks or months during the years 1947–1951. We are also harvesting a disheartening crop of late relapses in patients treated with resection followed by only short-term chemotherapy. It is never certain that all tubercle bacilli have been removed from the tuberculous host when the grossly involved lobe or segment is excised, nor can we postulate complete eradication of tubercle bacilli from the human host by any arbitrary period of drug treatment. In the light of these observations and accumulated experience with this disease, we believe that the time has come to explore *very* prolonged, perhaps life-long, treatment with antimicrobial agents. In a manuscript recently submitted for publication, we have presented data on 52 patients treated for periods of one to three years with various combinations of streptomycin, PAS, and isoniazid. There has been no instance of clinical or roentgenologic relapse in this group as of this date, and drug therapy is being continued and the program extended. The limitations of such a program have to do with patient acceptance, bacterial resistance, and drug toxicity. These factors are considered at greater length in our manuscript, but we wish to point out at this time the fact that patient acceptance of very prolonged chemotherapy (including the unpalatable PAS) is in direct proportion to the degree to which the physician is convinced of its importance, and to the zeal with which he transmits his belief to the patient. Final evaluation of this approach will require more prolonged observation of more patients, but up to now the results attained are gratifying and drug toxicity has not been a serious obstacle. The program is *not* recommended where adequate personnel and facilities for frequent laboratory and clinical evaluation are unavailable.

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ALFRED S. DOONEIEF
K. EILEEN HITE

February 17, 1954

Books

THORACIC SURGERY AND RELATED PATHOLOGY. By Gustaf E. Lindskog and Averill A. Liebow. Pp. 664, with illustrations, Appleton-Century-Crofts, Inc., New York, 1953, Price, $5.00.

For obvious reasons, postwar writers on thoracic surgery have been wary of entering the textbook field. It is a truism that, although the body of accurate medical knowledge constantly increases, old textbooks dealing with a given subject are frequently larger than modern ones. Sauerbruch's massive two-volume text and Lilienthal's were ponderous definitive works. The valuable volume of Graham, Singer, and Ballon published in 1935 reached 1,070 pages. As greater precision of knowledge is attained, economy of exposition is facilitated. It is easier to describe intratracheal anesthesia than the Sauerbruch or Willy Meyer chambers, and forty years of experience with thoracoplasty for tuberculosis provides a basis for succinct appraisal. A large variety of outmoded operations and procedures no longer deserve more than a footnote. Nevertheless, the growth of thoracic surgery in the past fifteen years has been such as to make authors avoid an attempt at the writing of a definitive textbook as too monumental a task, the fruits of which would be certain to be obsolete by the time of completion. As a result, the three or four books recently written have been brief, almost informal, descriptions of the scope of thoracic surgery.

The present work, by the Professors of Surgery and Pathology at Yale University, is an attractive volume. The thinking which this collaboration indicates has resulted in a readable text, modern in content and approach. It is formally organized as a textbook and, in view of its modest size (664 pages), is reasonably complete. The style is simple and lucid so that the book will be easily read by students and physicians not deeply versed in the problems of thoracic disease. Clinical descriptions of disease are satisfying and clear; many operative techniques are given in reasonable detail. There is a constant gratifying recourse to modern anatomic descriptions, the correlation of pathologic processes with the clinical picture, and the nature and measurement of physiological disturbance. The illustrations are abundant and well chosen. One regrets that modern publishing costs prevent the reproduction in color of an entire series of vinylite casts of bronchovascular anatomy.

Tuberculosis is still given a deservedly generous space, and the discussion ranges broadly over the therapeutic possibilities. It is pleasant to find pneumothorax and thoracoplasty not entirely discarded. Lung abscess and bronchiectasis, as vanishing diseases, are assigned less space than would have been permissible ten years ago. The section on the esophagus, like the rest of the work, is satisfying and complete within the limits of the space available. Cardiac surgery is similarly well treated in so far as the more usual procedures and conditions are concerned.

Inevitably, in a first edition, disproportion of space appears. Three pages are allotted to the technique of thoracentesis and more space is given to aspergillosis than to congenital cystic disease of the lung.

The easy, well-written historical introductions to most chapters add a good deal to the value of the book. The references to the literature and to the experiences of others are generally well chosen, if not exhaustive, and the bibliographies at the end of each chapter provide the classic references and a representative selection of the recent literature.

In establishing a systematic textbook format, chapter by chapter, the authors have

invited the comment that the arrangement lends itself to constant revision for future editions. Formal textbook organization of material is costly in space in that it requires some mention of almost everything. The smaller the work, the greater the unavoidable space expenditure of this kind. One may be allowed to hope that with future editions the work will assume definitive proportions and that the authors will allow themselves the luxury of more extensive treatment of subjects now included, as well as of those which will have gained importance with the passage of months.

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New York, New York

IMMUNITY, HYPERSENSITIVITY, and SEROLOGY. By Sidney Raffel. Pp. 531, Appleton-Century-Crofts, Inc., New York, 1953, Price, $8.00.

The concept of immunity almost automatically conjures up in our minds a series of interactions between antigens and antibodies specific for each infectious agent and for each noxious foreign substance. The spectacular success of transferable humoral antibodies in a limited and fairly understood group of infectious diseases inclines us to assume that the fundamental basis of all immune processes rests primarily on some sort of neutralization or disposal of the antigenic noxae through the specific antibodies elaborated against them by the invaded host. This is in harmony with the principle of least hypothesis, which is one of the cardinal cravings of the human mind and basic to the progress of scientific knowledge. It is not always possible, however, to achieve simplicity. It is the distinction of this thoughtful, clear, and comprehensive monograph to point out that not all pathogenic substances are antigenic and that not all antibodies which are detectable in an invaded host are necessarily directed against the nosogenic properties of the parasite.

In the first part of this volume, Dr. Raffel analyzes the concept of virulence. This is not merely the capacity of the invading parasite to multiply in the tissues of the host, but primarily its aptitude to exert noxious influences which disrupt the economy of the infected organism. It is the function of immunology, first, to seek out and identify the chemical entities existing either in the parasite itself or produced by it in the tissues of the host which are responsible for the pathogenic effects of the microorganisms; second, to characterize in each disease process the antibodies or other forces mobilized by the host which, in fact, counteract these nosogenic influences; and, finally, to ascertain the processes by which this is accomplished.

Much space is devoted to the elucidation of the process of formation of antibodies, their chemical and physical properties, their mode of interaction with antigens, and the specific roles that they play in the mechanism of immunity, when such is demonstrably the case. Dr. Raffel sets up criteria and postulates by which these substances can be gauged for the specific roles that they play in combating an infectious process. It is shown that, in many diseases, antibodies develop which thus far have not been demonstrated to play a significant role in disposing of the essential pathogenic effects of the parasite, and, therefore, play no real part in the mechanism of immunity against a given microorganism or virus.

Hypersensitivity is then pointedly discussed, sharply dissected, and skillfully integrated into the structure of the mechanism of increased resistance following reinfections. Dr. Raffel presents very clear evidence for the view that, particularly in tuberculosis, hypersensitivity is a process which is concomitant with the development of increased resistance but one that is quite distinct from, and independent of, the latter.

These two general sections of the book are followed by a consideration, in a number of

specific infectious diseases, of the chemical nature of the essential factors determining the pathogenicity of specific agents of disease, as well as by an appraisal of the processes, be they antigen-antibody interactions, or be they of another nature, which have at the moment been demonstrated to play a significant role in the immune response.

Dr. Raffel has succeeded in marshalling the essential and the most recent information available into an integrated concept in a manner which is enlightening and yet not burdened with superfluous details. The greatest value of the book is its challenge to the investigator to seek further and deeper into the mechanism of acquired resistance. This applies with particular emphasis to the field of tuberculosis, in which Dr. Raffel has labored with such success.

The book is highly recommended as a balanced critical estimate of the field of immunity, which, while not altogether free from personal views, yet is not marred by *ex cathedra* pronouncements which sometimes detract from works of this character.

MAX B. LURIE
Philadelphia, Pennsylvania

STUDIER ÖVER UROGENITALTUBERKULOSENS BEHANDLUNG. By Karl Ola F. Obrant. Pp. 159, Fran Kirurgiska Kliniken I Vid Sahlgrenska Sjukhuset, Goeteborg, 1953.

This report consists of the results of various therapeutic measures in 148 patients with urogenital tuberculosis.

Most of the patients were maintained on the conventional standard sanatorium supervision. All received a course of antituberculous chemotherapy. Specific operative procedures were performed on many of them.

The results of treatment were determined by three types of observations: roentgenographic studies, microbiologic studies of urine, and symptomatic improvement.

The routine roentgenographic examinations consisted of intravenous pyleogram and, only occasionally, a retrograde pyelogram. Cystoscopy examinations were comparatively rare because of the risk of possible spread of tuberculosis. Cystourethrographies and an occasional aortography were performed at the beginning of treatment.

The inoculation of urine into guinea pigs proved superior to Löwenstein medium cultures for demonstrating tubercle bacilli. In 283 urine examinations in which both tests were performed, 278 exhibited positive guinea pig inoculations, whereas only 34 showed positive urine cultures. In only 5 instances of positive urine cultures were the guinea pig inoculations negative.

The patients were divided into three categories with respect to the microbiologic data in the urine:

1. Stable "conversion" (for a period of at least four months, the last five guinea pig inoculations would have to have been negative for tubercle bacilli)
2. Uncertain "conversion" (the last five guinea pig inoculations have been negative for tubercle bacilli, but observations have been made for a period of less than four months)
3. Persistently positive

The chemotherapeutic agents used were streptomycin, para-aminosalicylic acid (PAS), and Conteben® (a thiosemicarbazone). Streptomycin was first given in a dosage schedule of 1 gm. daily, but later a regimen of 1 gm. every other day was adopted. Para-aminosalicylic acid was generally given in a dose of 10 gm. per day; and Conteben®, 0.005 gm. twice a day. In 48 per cent of the male patients and 35 per cent of the female patients, the treatment has exceeded one year.

All operative interventions with the exception of nephrectomy for pyonephrosis were preceded by a course of chemotherapy. The chemotherapy treatment was longest for partial nephrectomy; it lasted generally for approximately six months.

In regard to operative indications in renal tuberculosis, parenchymatous renal tuberculosis and minor unilateral ulcerous kidney lesions were not considered to indicate operative intervention. A heminephrectomy was carried out, however, if the renal lesion was in a position which would make this technically possible and when at least one-third of the kidney parenchyma appeared intact. Nephrectomy was carried out in cases of unilateral tuberculosis when the kidney showed an attendant marked decrease in function. In cases in which the ureter showed radiologic changes, the nephrectomy was combined with total ureterectomy. In cases of bilateral tuberculosis of kidneys, heminephrectomy was carried out if the localization was favorable. Tuberculous epididymitis was treated by epididymectomy. Tuberculous prostato-vesiculitis was not considered to be indicative of radical extirpation of these organs. If the epididymis was intact in cases of prostato-vesiculitis, a prophylactic vasectomy was carried out.

A group of 46 patients compiled from cases of unilateral renal tuberculosis without operation, bilateral renal tuberculosis, and tuberculosis of the remaining kidney after nephrectomy were treated for the most part without any surgical intervention on the kidneys. The exceptions to this were 9 instances of bilateral renal tuberculosis in which a nephrectomy or partial nephrectomy was performed. In this group of 46 patients, stable conversion of the urine was obtained in approximately 60 per cent. Twenty-five per cent continued to show tubercle bacilli in the urine, while the remainder obtained uncertain "conversion." The roentgenograms of the kidneys indicated improvement in all instances but 4. In all patients with bladder disturbances, symptoms disappeared or decreased considerably.

The group of 25 patients with unilateral tuberculosis underwent nephrectomy. Seventy-two per cent of this group obtained stable "conversion"; the urine remained persistently positive for tubercle bacilli in 8 per cent; and 20 per cent achieved uncertain "conversion." Genital tuberculosis and tuberculosis in the remaining kidney were the common findings in the group of patients with uncertain "conversions." The worth of chemotherapy was evident from the fact that the "conversion" in 7 instances in the latter group of patients was obtained after two to eleven months of postoperative antituberculous chemotherapy. Primary healing of the wound following nephrectomy occurred in 87 per cent; and, in 97 per cent, complete healing occurred within one month after operation.

Partial nephrectomy was carried out in 7 instances of unilateral and in 3 instances of bilateral renal tuberculosis. In 7 of these 10 cases, stable "conversion" of the urine was obtained. In 2 cases, an uncertain "conversion" was the result. It is thus seen, in terms of the microbiologic studies of the urine, that the results of the heminephrectomy were as good as total nephrectomy. In the nephrectomized patients, "conversion" was obtained more rapidly than in the nonoperated cases.

These studies show that chemotherapy must be of long duration in some cases; this was seen to be true in purely conservative treatment as well as in the operative cases. This was clearly evidenced by the histologic examination of the removed kidneys. The activity of the lesions from the removed kidneys was seen to be inversely proportional to the length of the course of preoperative chemotherapy.

The tuberculous bladder constituted a special problem, as it was inaccessible to chemotherapy. The operative interventions employed were uretero-sigmoidostomy, cutaneous ureterostomy, and resections of nervi hypogastrici. The cutaneous transplants have proved to be superior to the transplants into the intestine.

Tuberculosis in the male genital organs without a known coexistent urinary tuberculosis occurred in 30 instances. Semen analysis and cytologic semen examination proved to be of great diagnostic aid as well as establishing indications for prophylactic vasectomy. "Positive" guinea pig inoculations from the semen have sometimes been obtained. Stable "conversion" was obtained in approximately 50 per cent of the patients with genital tuberculosis, 25 per cent showed urine cultures persistently positive for tubercle bacilli, and the rest showed uncertain "conversion." It was evident from this material that tuberculous lesions in the prostate and seminal vesicles remain active despite a coexistent stable "conversion" of the urine. In 20 cases of genital pelvic lesions, the prophylactic vasectomy has provided an effective protection for the epididymis. Healing of the wound after epididymectomy was primary in 81 per cent of the cases.

Relapses occurred in 17 of the total group of 148 patients. Of these 17 patients, 15 were males with evidence of genital tuberculosis and 2 were females.

The possible emergence of tubercle bacilli resistant to the chemotherapeutic agents used has been investigated. Despite long treatment, no such resistance could be determined. This was attributed to the fact that streptomycin and Conteben® for the most part were used in combination with PAS.

After surgery, all patients continued to receive chemotherapy until stable "conversion" of the urine was obtained. If the desired results with the above chemotherapeutic agents were not obtained after six months, the patient was also given isoniazid in combination with streptomycin and/or PAS.

Following discharge from the hospital, the patients were placed under the care of medical officers for urine tests with guinea pig inoculations.

There are sixteen diagrams, four tables, eleven figures, and two hundred and ninety-five references.

M. Sierp
New York, New York

BOOKS RECEIVED

Röntgenanatomische Grundlagen der Lungenuntersuchung. By F. Kováts, Jr., and Z. Zsebök. Pp. 287, with illustrations, Akademiai Kiado, Budapest, 1953.

Lung Cancer. By Seymour M. Farber. Pp. 162, with illustrations, Charles C Thomas, Springfield, Illinois, 1954, Price, $4.75.

BCG Vaccination in Egypt, 1949–1952, with special reference to Statistics on BCG Vaccination and Pre- and Post-Vaccination Allergy. Pp. 55, The International Tuberculosis Campaign, UNICEF, 24 Rue Borghèse, Neuilly-sur-Seine, France, 1953.

American Trudeau Society

Medical Section of the National Tuberculosis Association

Report of Tenth Pembine Conference

The annual Pembine Therapy Conference was held at the Four Seasons Club, Pembine, Wisconsin, on September 11, 12, and 13, 1953. Minnesota and Wisconsin were represented by fifteen conferees each, and Michigan by twenty conferees. The ten guests from outside the tri-state area were:

Oscar Auerbach	East Orange, N. J.
John B. Barnwell	Washington, D. C.
David A. Cooper	Philadelphia, Pa.
Roberts J. Davies	Seattle, Wash.
Fred J. Jarvis	Seattle, Wash.
William M. Lees	Chicago, Ill.
Edward L. Ross	Winnipeg, Man.
Paul C. Samson	Oakland, Calif.
Jesse A. Stocker	Springfield, Ill.
James J. Waring	Denver, Colo.

Drs. Davies and Jarvis were the guest presenters. There were no formal papers this year.

The major section of the Conference was the presentation by selected hospitals of fifty consecutive admissions on and after July 1, 1952. These hospitals were:

Michigan —Pinecrest Sanatorium, Powers
Minnesota—Glen Lake Sanatorium, Oak Terrace
Wisconsin—State Sanatorium, Wales
Guest —Firland Sanatorium, Seattle, Wash.

There was a deviation from past years in that the hospitals selected were not comparable in size but, instead, served differing types of population areas and were operated under different governmental units. However, the four series of cases were quite comparable with respect to patients and to the extent and variety of pathology.

The differences between the series proved to be stimulating and to emphasize many problems which have not been resolved. Some of these have a definite bearing on therapy. The large hospitals have well-rounded staffs and carry out all phases of the treatment, whereas the smaller hospitals frequently must transfer patients for many specialized procedures.

There was a more conservative attitude toward therapy than had existed at previous Conferences. Less stress upon resectional surgery and greater emphasis upon prolonged chemotherapy were evident. These combined to give a more critical aspect to the Conference. The questions that recurred during the presentations were:

How long should drug therapy be continued?
How much can bed rest be modified with chemotherapy?
What types of lesion should be resected, what types might be treated by other surgical procedures, and what types can be left alone?

The majority of the Conference believed that combinations of two drugs were adequate and desirable, since there is no evidence that combinations of three or four drugs produce significant differences. Most conferees preferred to have effective drugs in re-

serve for emergency use or for those patients showing clinical resistance to previously used agents. Therapy with multiple drugs presents added problems when toxic manifestations appear. Combinations of streptomycin with para-aminosalicylic acid or with isoniazid were used most commonly. Isoniazid was considered a major therapeutic agent, its place in therapy being enhanced steadily by experience.

The trend definitely was toward more prolonged therapy. Six to eight months of therapy before surgery was favored in the average case. The over-all period of drug therapy varied from one year to "as long as the patient will accept it." The majority considered eighteen to twenty-four months as probably adequate. It was apparent that considerable uncertainty existed on this point. There was a stated willingness to overtreat, rather than risk inadequate therapy.

The predominant surgery in all of the series was resection. The Conference, however, was much more critical this year, particularly in cases of limited involvement. This could be related directly to the changing attitude toward prolonged drug therapy. All agreed that a critical review of operated cases, with an adequate control group, was needed to establish more definite indications for resection. There was not much question about resecting extensive areas of destroyed lung; there was considerable question about removing small, nodular lesions.

The medical members felt they should have more say in the selection of cases for surgery. The surgeons countered that the medical staff was prone to crowd the surgeons to accept extremely risky cases. The surgeons also felt that longer periods of bed rest postoperatively were desirable. This and other discussions emphasized the need for the highest degree of cooperation. It was summarized quite well by one conferee who stated, "it is doubtful if the successful understanding and treatment of any disease other than tuberculosis is more dependent upon close correlation of clinical, surgical, radiological, bacteriological, pathological and physiological judgments."

There were three forms of tuberculosis which generated discussion concerning the therapy. Almost all agreed that tuberculous pleurisy with effusion should receive chemotherapy, with a year's therapy being favored. Most agreed that demonstrable tuberculosis, either lymphatic or parenchymal, in children deserved intensive therapy. The Conference felt that tuberculosis in children was considered a more serious disease by phthisiologists than by pediatricians. There was considerable difference of opinion regarding the proper treatment of recent tuberculin "converters." One group held that such persons should be given chemotherapy on an ambulatory status, using isoniazid as the drug of choice. On the other side were those who preferred to wait and treat only those who developed clinical disease. As the discussions were based primarily upon opinions rather than clinical experiences, no definite conclusions were reached.

The second portion of the Conference was an innovation. Twenty consecutive cases of pneumothorax initiated in 1943 and continued for more than one year had been presented by each of three hospitals at the 1946 Conference. These cases were again presented this year by the same physicians.

Michigan —Northern Michigan Tuberculosis Sanatorium, Gaylord
Minnesota—Nopeming Sanatorium, Nopeming
Wisconsin—Muirdale Sanatorium, Milwaukee

It is remarkable that the current status of all these patients is known! Five of the cases were minimal; 36, moderately advanced; and 20, far advanced. Fifty-five of the patients are alive, with 3 classed as having active disease. Of the 6 deaths, 3 were from nontuberculous causes. This was a selected group in that all had had at least one year of continuous pneumothorax, so more favorable results could be anticipated. They would not

reflect the over-all experience with the therapy. Several of the patients had surgical procedures subsequent to their pneumothorax.

The discussions were most interesting. Those who had extensive experience with pneumothorax spoke approvingly of the procedure. It was pointed out that many of the serious complications of pneumothorax could be minimized now with antimicrobials. Other procedures used at present are more effective and satisfactory. The feeling was that pneumothorax may have a place, but the place cannot be defined at this time.

The final group of cases presented from each state consisted of 10 cases of recurrence of disease after resectional surgery. Criteria for selection had been established. The cases selected were those showing roentgenographic exacerbations in the same lobe or the same lung in which surgery had been done, since the status of the disease at the time of surgery would be known. Reactivations appearing in the contralateral lung or manifested only by a "positive sputum" were acceptable. Considerable difficulty was encountered by each state committee in accumulating its 10 cases. Very few of the requested types were found. The ratio of these cases to the total of the operated cases was quite low.

The cases showing roentgenographic evidence of exacerbation most frequently displayed bacterial resistance or inadequate therapy. The latter included patients treated for only a few weeks or those whose therapy had been interrupted. Relapse in the majority of the cases was predicated upon positive bacteriology alone. These showed frequently ulcerative changes in the bronchial stump. Most "converted" with continued therapy. A justifiable criticism was that other patients had received comparable therapy and had responded satisfactorily. No conclusions could be derived from this small series except that recurrence seems to be infrequent.

The next Pembine Conference was scheduled for September 10, 11, and 12, 1954.

Joseph L. Egle, Michigan
Arthur M. Olsen, Minnesota
Morris C. Thomas, Wisconsin
Chairman, Pembine Conference

Obituaries

ORANGE V. CALHOUN

1901–1953

Orange V. Calhoun of Lincoln, Nebraska, died on November 3, 1953, after a very sudden illness at the age of fifty-two. He is survived by his wife, Marjorie T. Calhoun, his daughters, Jane Ann and Mary Lou, and his son David, his mother, and three brothers. He practiced medicine in the city of Lincoln, Nebraska, for nineteen years.

Dr. Calhoun was president of the Lancaster County Tuberculosis Society for two years; was past president of the Lincoln-Lancaster Health Department, a member of the State and National Medical Associations, the Board of Internal Medicine, and the American Trudeau Society. In 1938 he was made a life member of the American College of Physicians. He was a veteran of the Second World War and was in the Naval Reserve. He was a past member of the Board of Education; was active in the Lincoln Chamber of Commerce, Rotary, Candlelight Club, Social Welfare Society, University Club, and Country Club. He was a collector of rare medical books.

Dr. Calhoun was born in Birmingham, Iowa, February 6, 1901. He received his Bachelor of Science degree from Iowa Wesleyan University in 1926, did graduate work later at Johns Hopkins University, received his Doctor of Medicine degree from Western Reserve University in 1932, and interned at Lakeside Hospital. At the time of his death he was Chief of the Medical Service at the Veterans Hospital in Lincoln, Nebraska.

E. B.

JOSEPH H. SCHULTZE

1907–1953

Joseph H. Schultze of Birmingham, Alabama, died of coronary thrombosis on September 3, 1953, at the age of forty-six. He was a native of Fort Mitchell, Kentucky. He received his Bachelor of Science degree from the University of Dayton, and, in 1934, his Doctor of Medicine degree from the University of Louisville. He became interested in the tuberculosis problem while a student at the University of Louisville. After serving as a captain in the Medical Corps during World War II, he returned to his first interest, and became a member of the American Trudeau Society. He served on the staff of American Legion Hospital, Battle Creek, Michigan; Marianna Tuberculosis Sanatorium in Marianna, Florida; the Mississippi State Sanatorium in Sanatorium, Mississippi; and, at the time of his death, was Assistant Superintendent of the Jefferson Tuberculosis Sanatorium, Birmingham, Alabama.

E. B.

BENJAMIN E. GOODRICH

1900–1953

Benjamin E. Goodrich received his medical degree in 1926 from State University of Iowa, College of Medicine. He was a Fellow in the American Medical Association; a member of the Central Society for Clinical Research, the American College of Chest Surgeons, and the American Trudeau Society; a Fellow of the American College of Physicians and Diplomate of the American Board of Internal Medicine. He served during World War I and World War II. He died in Pleasant Ridge, Michigan, June 15, 1953, at the age of fifty-three of coronary occlusion. At that time he was Chief, Pulmonary Division, Henry Ford Hospital, Detroit, Michigan.

E. B.

LOREN L. COLLINS

1890–1953

Loren L. Collins, of Edwardsville, Illinois, born in Wilkes-Barre, Pennsylvania, October 24, 1890, died May 1, 1953 at the age of sixty-three. He received his medical degree in 1925 from the University of Illinois, College of Medicine, Chicago. Dr. Collins obtained his license in 1925. He was resident physician at Minneapolis General Hospital, resident in pediatrics at Illinois Research Hospital, staff physician at Chicago Municipal Tuberculosis Hospital, and medical director of LaSalle and DeKalb Counties Tuberculosis Sanatoria. He was past president of the Mississippi Valley Trudeau Society, was a Fellow of the American Medical Association, and a member of the American Trudeau Society. His professional activities were in the field of pulmonary diseases. At the time of his death he was medical director and superintendent of Madison County Sanatorium, Edwardsville, Illinois.

E. B.

CHARLES McCHRISTIE HENDRICKS

1878–1953

Dr. Charles McChristie Hendricks of El Paso, Texas, died of cancer on December 9, 1953, at the age of seventy-five. He received his M.D. degree in 1905 from Medical College of the University of Ohio, Cincinnati, Ohio. He was made an honorary member of the Texas Medical Association in 1952, with membership since 1908. He was past president of the El Paso County Medical Society, chairman of the Committee on Tuberculosis of the Texas Medical Association, a member of the American Medical Association, and past president of the American College of Chest Physicians. In 1948 he was awarded its medal for furthering progress in the field of diseases of the chest. He was a member of the American Trudeau Society, an honorary life member of the Pan American Medical Association, a member of the United States Committee of World Medical Association, director of Research and Education Council of College of Chest Physicians, and executive director of the Common Cold Foundation. He was the first editor of Diseases of the Chest and former medical director of Baldwin and El Paso sanatoriums and Hendricks-Laws Sanatorium, which he founded. He practiced medicine in El Paso for forty-six years.

A colonel in the United States Army Reserve Medical Corps, Dr. Hendricks served during World War I as a lieutenant colonel with the Ninetieth Regiment in San Antonio, Europe, and with the Army of Occupation in Germany. He was a member of Phi Delta Theta fraternity, Sons of the American Revolution, charter member of El Paso Rotary Club, an honorary member of Kiwanis, a member of the Masonic Order, past chairman of the American Red Cross in El Paso, past president of the Gate Way Club, a founder of the Sun Carnival Association, and a member of the Presbyterian Church. His death brought deep sadness to his family, his associates, and his community.

E. B.

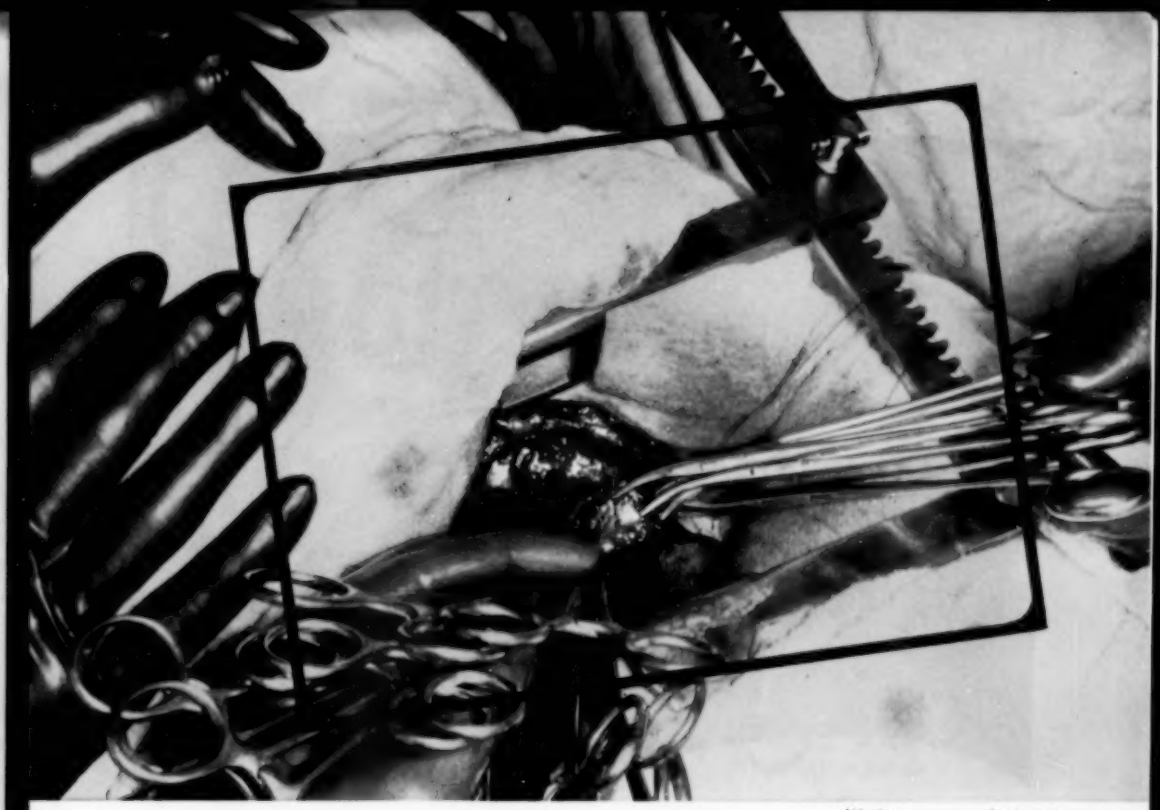
ROBERT G. McCORKLE

1892–1954

Robert G. McCorkle died on March 20, 1954, in San Antonio at the age of sixty-two. He received his medical degree in 1916 from the Baylor University College of Medicine and served on the staffs of Santa Rosa, Robert B. Green, Mix Memorial, and Baptist Memorial Hospitals. He was a member of the American Board of Internal Medicine and

of the Texas, Southern, and American Medical Associations. He was a consultant in diseases of the chest at the Army's Brooke Medical Center, a member of the American College of Physicians, the National Tuberculosis Association, the American Trudeau Society, American College of Chest Physicians, a Fellow of the American College of Physicians, a director of the Texas Tuberculosis Association, and one of the organizers and the first president of the Bexar County Tuberculosis Association. At the time of his death he was medical superintendent of The Woodmen of the World Tuberculosis Hospital and chairman of the San Antonio-Bexar County Tuberculosis Control Board.

E. B.



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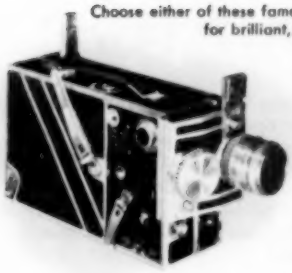

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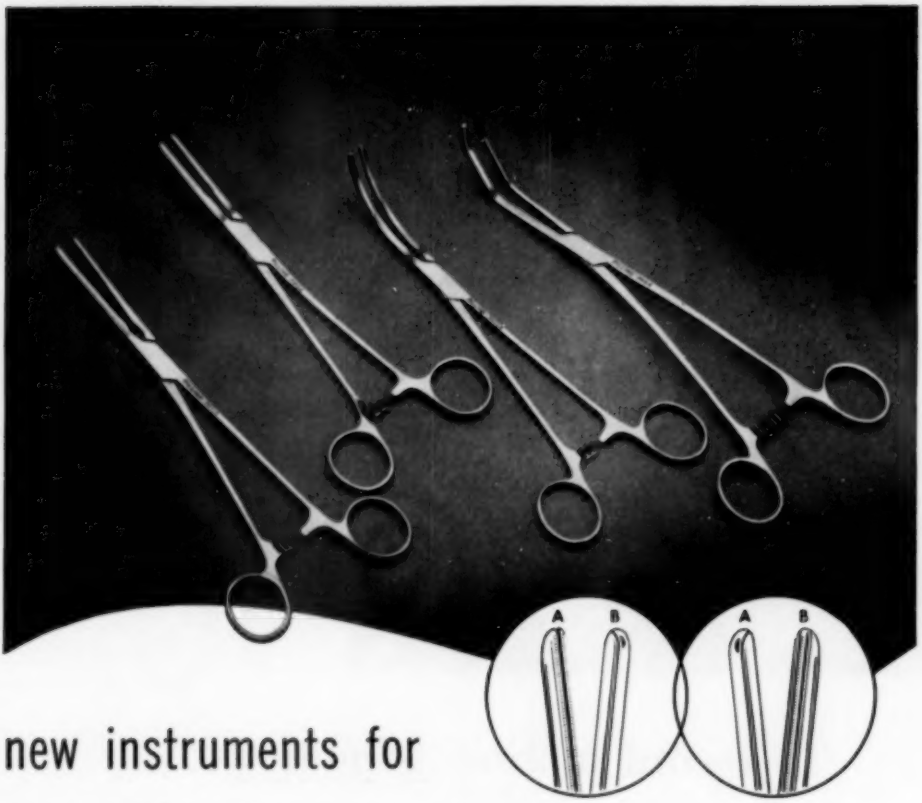

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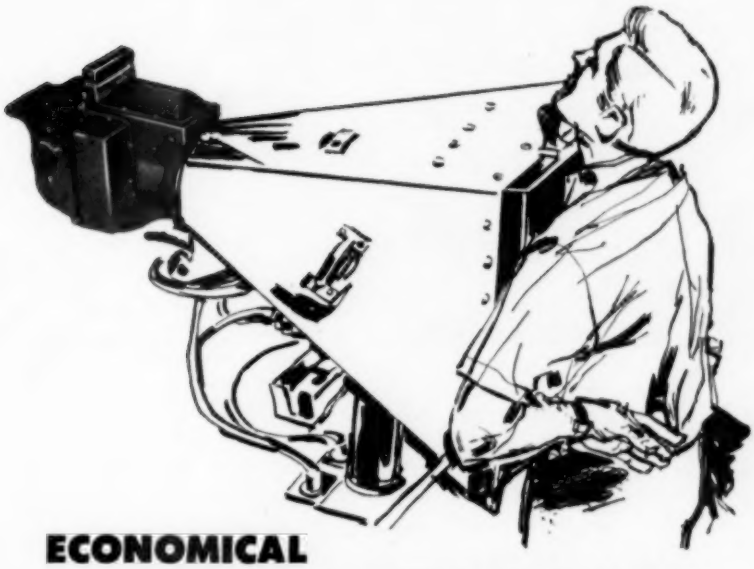

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